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Health and Environmental Effects Profile for N,N-Dimethylformamide

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16. ABSTRACT

The Health and Environmental Effects Profile for N,N-Dimethylformamide was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. N,N-Dimethylformamide has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for N,N-dimethylformamide is 0.096 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for N,N-dimethylformamide is 100.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR N,N-DIMETHYLFORMAMIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constit- uents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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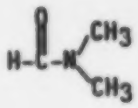
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BOD	Biochemical oxygen demand
CS	Composite score
DMSO	Dimethyl sulfoxide
EC_{50}	Concentration that results in a 50% reduction in light input
ECG	Electrocardiograph
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MATC	Maximum Acceptable Toxin Concentration
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEC	No-effect concentration
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister-chromatid exchange
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TL_M	Median tolerance limit
UDS	Unscheduled DNA synthesis
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

N,N-Dimethylformamide is the common chemical name of the compound also known as DMF or dimethylformamide. The structure, molecular weight, empirical formula and CAS Registry number for dimethylformamide are as follows:



Molecular weight: 73.09

Empirical formula: C_3H_7NO

CAS number: 68-12-2

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Dimethylformamide is a colorless, hygroscopic liquid with a faint but characteristic odor (Eberling, 1980). It is completely miscible with water, alcohol, ether, acetone, benzene and chloroform but not with aliphatic hydrocarbons. A list of selected physical properties of dimethylformamide follows:

Freezing point:	-61°C (Eberling, 1980)
Boiling point:	153°C (Eberling, 1980)
Density at 25°C:	0.9445 g/cm³ (Eberling, 1980)
Refractive index, 25°C:	1.4269 (Eberling, 1980)
Vapor pressure:	
20°C	2.7 mm Hg (Verschueren, 1983)
25°C	3.7 mm Hg (U.S. EPA, 1981)
Vapor density (air=1.0)	2.51 (Verschueren, 1983)
Flash point:	58°C (Eberling, 1980)

Log octanol/water partition coefficient:	-1.01 (Hansch et al., 1972) -0.87/-0.59 (Verschueren, 1983) (calculated)
Conversion factors: (air) at 20°C	1 mg/m³ = 0.33 ppm 1 ppm = 3.04 mg/m³

Violent reactions can result from exposure of dimethylformamide to nitrates, chromic acid, or triethylaluminum (Eberling, 1980). At room temperature, dimethylformamide dissolves various salts (Eberling, 1980).

1.3. PRODUCTION DATA

Production data available from U.S. EPA (1977) are listed in Table 1-1; Du Pont alone reported the manufacture of 50-100 million pounds. United States production for 1979 was estimated to be ~30 million pounds (Eberling, 1980).

Only two United States companies are cited as manufacturers of dimethylformamide as of January, 1985 (SRI, 1985): Air Products and Chemicals, Inc. in Pensacola, FL, and Du Pont in Belle, WV.

Dimethylformamide is commonly manufactured by one of two methods: (1) a one-stage reaction of carbon monoxide with dimethylamine or (2) a two-stage reaction in which carbon monoxide is first reacted with methanol to form methylformate, which is then reacted with dimethylamine to yield dimethylformamide (Eberling, 1980).

1.4. USE DATA

The use pattern for dimethylformamide has been estimated as follows (Eberling, 1980):

Solvent for acrylic fibers and polyurethanes	65-75%
Production (crystallization solvent) of pharmaceutical products	15-20%
Miscellaneous uses including pesticides	remainder

TABLE 1-1

Dimethylformamide Production Data for 1977*

Company	Type of Production	Production Range (pounds)
Air Products & Chem. Pace, FL	manufacturer	confidential
E.I. Du Pont, Belle, WV	manufacturer	50-100 million
BASF Wyandotte Parsippany, NJ	importer	confidential
Atlantic Chem. Nutley, NJ	importer	10-100 thousand
A & S Corp., Morris, NJ	importer	10-100 thousand
Thorson Chem. New York, NY	importer	<1000
M & T Chem Stamford, CT	importer	confidential
Phillips Bros. Chem. New York, NY	importer	confidential
GAF Corp., New York, NY	importer	<1000
Rohm & Haas Co. Philadelphia, PA	importer	10-100 thousand
Ciba-Geigy Corp. Ardsley, NY	importer	none
Eastman Kodak Rochester, NY	importer	none
ICI Americas Wilmington, DE	importer	10-100 thousand
Carroll Products Wood River Junction, RI	confidential	none
Eastman Kodak Rochester, NY	confidential	confidential

*Source: U.S. EPA, 1977

Dimethylformamide is used primarily as an industrial solvent. Dimethylformamide solutions are used to process polymer fibers, films and surface coatings, to permit easy spinning of acrylic fibers, and to produce wire enamels. The pharmaceutical industry uses dimethylformamide as a crystallization medium for vitamins, hormones and sulfonamides (Eberling, 1980). Other uses include solvent use in electrolytic capacitors and electroplating baths, in the extraction of hydrocarbons such as acetylene and 1,3-butadiene, in the extraction of H_2S and SO_2 from flue gases and aromatics from petroleum streams, and as a paint stripper and cleaner (Eberling, 1980; U.S. EPA, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Aqueous solutions of dimethylformamide undergo slight hydrolysis at neutral pH (only 0.17% of a 50% solution was hydrolyzed after 120 hours of refluxing); however, hydrolysis is accelerated by acids and bases (Eberling, 1980). Hydrolysis rate data for acid- or base-catalyzed reactions could not be located in the available literature as cited in the Appendix.

2.1.2. Oxidation. Pertinent data regarding oxidation of dimethylformamide in the aquatic environment could not be located in the available literature as cited in the Appendix.

2.1.3. Photolysis. The UV absorption spectra for dimethylformamide shows no absorption >290 nm (Grasselli, 1973); therefore, direct photolysis of dimethylformamide will not occur in the environment. Pertinent data regarding the potential for photosensitized degradation of dimethylformamide could not be located in the available literature as cited in the Appendix.

2.1.4. Microbial Degradation. Doljido (1979) found dimethylformamide to be biodegradable under several testing conditions. In an activated sludge system, 100% (70 mg/ℓ) was degraded in 38 days. With acclimated sludge seed, 91% of the theoretical BOD for dimethylformamide was found to degrade in 6-10 days with a 3-day lag at 80 mg/ℓ and a 4.5 day lag at 440 mg/ℓ. A river die-away test under light aeration conditions has shown that dimethylformamide (28 mg/ℓ) was degradable in water with a lag time of 2 days. The lag time decreased with the acclimatization of microorganisms (Doljido, 1979).

Gubser (1969) used a continuous-flow activated sludge system to determine that dimethylformamide was 90-100% degradable with lag periods of 10 days at concentrations of 20 and 50 mg/ℓ and 28 days at a concentration of 81 mg/ℓ. Other researchers have also found dimethylformamide degradable in activated sludges, although the rate of degradation may be slow with certain sludges (Thonke and Dittman, 1966; Carter and Young, 1983; Boszczyk-Maleszak and Bieszkiewicz, 1982; Houser et al., 1983; Chudoba et al., 1969; Kalmykova and Rogovskaya, 1978; Begert, 1974, 1975; Nakajima, 1970). Pseudomonas sp., isolated from sewage effluent, were able to degrade dimethylformamide after a lag-period of ~25 minutes (Focht and Joseph, 1971). Pseudomonas sp. II and Vibrio aeromonas, isolated from activated sludge, were able to grow on dimethylformamide as sole sources of carbon and nitrogen (Bodzek and Kominek, 1979). Chromek et al. (1983) found that non-adapter cultures of the alga, Scenedesmus quadricauda, were able to degrade dimethylformamide to dimethylamine.

2.1.5. Volatilization. Pertinent data regarding volatilization of dimethylformamide could not be located in the available literature as cited in the Appendix. Henry's Law constant at 20°C can be calculated from the vapor pressure of dimethylformamide (2.7 mm Hg) and the water solubility (assumed to be 10^6 ppm for complete miscibility) to be $\sim 2.6 \times 10^{-7}$ atm-m³/mol. This value indicates that dimethylformamide will not volatilize from the aquatic environment to any significant extent (Lyman et al., 1982).

2.1.6. Adsorption. Pertinent data regarding the adsorption of dimethylformamide could not be located in the available literature as cited in the Appendix. The complete water solubility and low octanol/water partition

coefficient of dimethylformamide, however, suggests that adsorption to particulate organic matter and sediments in water is not likely to have importance as an environmental process.

2.1.7. Bioaccumulation. Sasaki (1978) used the Japanese MITI test to determine that dimethylformamide does not bioaccumulate in fish (carp). This test is performed with a ratio of dimethylformamide to activated sludge of 100:30 ppm at 25±2°C, pH 7.0 for 2 weeks. The complete water solubility and low octanol/water partition coefficient (log P = -1.01) of dimethylformamide suggest that it will not bioconcentrate significantly.

2.2. AIR

2.2.1. Chemical Removal Processes. Pertinent data regarding the reaction rate of dimethylformamide with hydroxyl radicals, with other atmospheric radicals or with ozone could not be located in the available literature as cited in the Appendix. Darnall et al. (1976) reported that dimethylformamide is expected to be relatively nonreactive with hydroxyl radicals in the atmosphere (when compared with other hydrocarbons) because it has a disappearance half-life of >9.9 days in a polluted atmosphere with an assumed OH concentration of 10^7 radicals/cm^3. If a typical atmosphere has a concentration of 10^6 OH radicals/cm^3, the half-life of dimethylformamide is expected to be >99 days. In smog chamber studies, dimethylformamide was relatively nonreactive in regard to photochemical oxidant formation (Sickles et al., 1980; Laity et al., 1973; Farley, 1977).

As indicated in Section 2.1.3., the UV absorption spectra for dimethylformamide shows no absorption >290 nm (Grasselli, 1973); therefore, direct photolysis in the atmosphere is not expected to occur.

2.2.2. Physical Removal Processes. Pertinent data regarding the atmospheric removal of dimethylformamide by wet deposition or adsorption onto

aerosol particles could not be located in the available literature as cited in the Appendix. The complete water solubility of dimethylformamide suggests that removal either by dissolution into clouds and subsequent rainfall or by the scrubbing effect of rainfall itself is a potentially important process.

2.3. SOIL

2.3.1. Microbial Degradation. Romadina (1975) isolated a bacteria culture (not specified) from soil that was in contact with small amounts of petroleum and petroleum products for several years. When wastewater containing 250 mg/L dimethylformamide was aerobically treated with this culture and activated sludge, 95% of the dimethylformamide was degraded in 18 hours of treatment.

2.3.2. Chemical Degradation. Pertinent data regarding the chemical degradation of dimethylformamide could not be located in the available literature as cited in the Appendix.

2.3.3. Leaching. Experimental soil adsorption data could not be located in the available literature as cited in the Appendix. However, the miscibility with water and the low octanol/water partition coefficient (log P = -1.01) of dimethylformamide suggest that leaching into soil, and potentially into groundwater, is possible. The molecular topology and quantitative structure-activity relationship analysis method of Sabljic (1984) predicts that dimethylformamide will have a soil sorption coefficient of ~50, which also indicates that dimethylformamide is expected to have a high mobility in soil.

2.3.4. Volatilization. Pertinent data regarding the volatility of dimethylformamide could not be located in the available literature as cited in the Appendix. The vapor pressures of dimethylformamide at 20°C (2.7 mm

Hg) and 25°C (3.7 mm Hg) suggest that evaporation from dry soil surfaces could be significant, whereas in moist soils leaching could restrict evaporation and become the dominant transport process.

2.4. SUMMARY

Dimethylformamide is susceptible to biodegradation by activated sludges, although an acclimation period is usually required. Water from the Vistula River has been reported to biodegrade dimethylformamide, as has an unspecified bacteria culture isolated from soil exposed to petroleum and petroleum products.

Dimethylformamide does not absorb UV radiation >290 nm; therefore, direct photolysis in the environment should not occur.

In the aquatic environment, dimethylformamide adsorption to particulates and sediment and dimethylformamide volatilization are not significant processes. Dimethylformamide hydrolyzes slowly in neutral pH water, but hydrolysis is accelerated by acids and bases. The bioaccumulation of dimethylformamide in aquatic organisms is reported to be insignificant.

Pertinent data regarding the removal of dimethylformamide from the atmosphere could not be located in the available literature as cited in the Appendix. The half-life disappearance rate in a polluted atmosphere of 10^7 hydroxyl radicals/cm^3, however, has been estimated to be >9.9 days. Removal by rainfall may have some importance as dimethylformamide is completely miscible with water.

Dimethylformamide is expected to be susceptible to leaching (high mobility) in many kinds of soil.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base listed one observation regarding dimethylformamide: a concentration of 2 µg/ℓ was detected in a sample taken from the Calumet sewage treatment plant on the western shore of Lake Michigan on December 12, 1975. Shackelford and Keith (1976) reported that dimethylformamide was found in the effluent from a U.S. sewage treatment plant (not identified); concentrations were not reported, but this citation may be identical to the observation in STORET.

Perry et al. (1979) collected and analyzed water samples from 63 effluent and 22 intake waters from chemical manufacturers throughout the United States for organic pollutants. Dimethylformamide was detected in only one sample (location not reported) at a concentration <10 µg/ℓ. Ewing et al. (1977) examined 204 water samples obtained from 14 heavily industrialized river basins in the United States between August, 1975 and September, 1976. Dimethylformamide was detected in only one sample (from the Delaware River basin) at a concentration of 2 ppb.

Dojlido (1977) detected dimethylformamide in effluent from a Polish plant manufacturing synthetic leather. Dimethylformamide was also detected in discharge water from a lagoon-type chemical waste treatment plant (concentrations not reported) and in water discharged into Lake Tahoe from a municipal sewage treatment system (U.S. EPA, 1981).

3.2. FOOD

Pertinent data regarding the exposure to dimethylformamide through foods could not be located in the available literature as cited in the Appendix.

3.3. INHALATION

Dimethylformamide is emitted into the atmosphere from industrial sources and during its use as a solvent (Graedel, 1978). Amster et al. (1983) monitored atmospheric concentrations of dimethylformamide at a chemical waste reclamation plant and in the neighboring industrial and residential communities and found levels of 2.18, >50 and 8 ppb, respectively. Kotlovoi et al. (1979) reported that dimethylformamide used in the production of synthetic fibers represents a source of pollution from ventilation system emissions.

Dimethylformamide can form in sunlit atmosphere by photooxidation of dimethylamine or trimethylamine (Pitts et al., 1978).

NIOSH (1981) estimates that 69,191 workers are exposed annually to dimethylformamide. Workplace monitoring studies conducted over a 2-year period in a British chemical plant found airborn concentrations as high as 200 ppm; however, the majority of measurements were <10 ppm (U.S. EPA, 1981).

4. PHARMACOKINETICS

4.1. ABSORPTION

Limited information regarding the rate and extent of absorption of dimethylformamide from the GI tract is available. An abstract of a Russian study reported that concentrations of dimethylformamide in the blood of rats during 24 hours following oral treatment at 4-4000 mg/kg were proportional to the dose (Sanotskii et al., 1978). Additional details were not provided.

Dimethylformamide is rapidly absorbed by the pulmonary and dermal routes. Peak blood and tissue levels of dimethylformamide (Section 4.2.) were reached within 0-3 hours following exposure of rats in a chamber to 565 and 2250 ppm (1689 and 6726 mg/m³) (Lundberg et al., 1983). The concentration of dimethylformamide in the blood of four humans (3 males and 1 female) immediately following 2-hour inhalation exposure to 53±32 ppm (158±96 mg/m³) dimethylformamide was 9.9 µg/mL (Eben and Kimmerle, 1976). The range of concentrations in the blood was 7.1-13.9 µg/mL. Massmann (1956) reported that rats whose tails were dipped into 100% dimethylformamide for 8 hours absorbed at least 0.8 mL through 14 cm² of exposed skin, which is equivalent to ~0.06 mL/cm² or 57 mg/cm².

4.2. DISTRIBUTION

Lundberg et al. (1983) studied the distribution with time of dimethylformamide and its metabolite, detected by GC as monomethylformamide (Section 4.3.), in female Sprague-Dawley rats following a 4-hour exposure to 565 or 2250 ppm (1689 or 6726 mg/m³) (Table 4-1). Following the low exposure (565 ppm), tissue and blood levels of dimethylformamide declined rapidly in the first 3 hours and were no longer detectable at 20 hours. Levels of the metabolite rose slightly over the first 6 hours after exposure but were not detected at 20 hours. Following the high exposure, blood and tissue levels

TABLE 4-1

Tissue Concentrations of DMF and MMF at Different Times After a 4-Hour Exposure of Rats to DMF[a,b]

Time After the End of Exposure (hours)	2250 ppm Exposure					565 ppm Exposure				
	Blood (μmol/mL)	Liver (μmol/g)	Kidney (μmol/g)	Brain (μmol/g)	Adrenals (μmol/g)	Blood (μmol/mL)	Liver (μmol/g)	Kidney (μmol/g)	Brain (μmol/g)	Adrenals (μmol/g)
Concentration of DMF										
0	13.2±0.4	9.8±0.5	11.0±0.8	11.4±0.7	8.6±0.4	5.1±0.8	2.8±0.3	3.1±0.4	3.1±0.8	2.1±0.2
3	14.9±1.3	11.7±0.9	12.8±0.8	12.7±0.9	8.8±0.6	2.8±0.2	1.8±0.1	2.8±0.7	2.0±0.1	1.6±0.2
6	13.0±0.5	10.1±0.2	11.5±0.5	10.1±1.8	9.0±0.4	2.7±0.4	1.8±0.5	2.0±0.4	1.9±0.4	1.5±0.6
20	3.6±0.4	2.6±0.3	3.1±0.5	1.5±0.3	1.9±0.1	<0.4	<0.5	<0.6	<0.3	<0.9
48	<0.4	<0.2	<0.6	<0.3	<0.9	<0.4	<0.5	<0.6	<0.3	<0.9
Concentration of MMF										
0	<0.4	<0.3	0.8±0.1	0.4±0.0	<1.0	0.7±0.0	0.5±0.1	0.9±0.1	0.5±0.1	<1.0
3	<0.4	0.5±0.0	<0.6	<0.3	<1.0	0.8±0.0	0.5±0.1	0.9±0.1	0.6±0.0	<1.0
6	1.2±0.1	0.7±0.0	1.3±0.3	0.5±0.0	1.2±0.2	0.8±0.1	0.6±0.0	1.2±0.1	0.7±0.0	1.0±0.1
20	5.0±2.0	1.9±0.4	2.3±0.2	2.1±0.2	1.9±0.1	<0.4	<0.3	<0.6	<0.3	<1.0
48	<0.4	<0.3	<0.6	<0.3	<1.0	<0.4	<0.3	<0.6	<0.3	<1.0

[a]Source: Lundberg et al., 1983

[b]Results are presented as mean ± SE (n=4)

DMF = Dimethylformamide; MMF = metabolite detected as monomethylformamide by gas chromatography

of dimethylformamide remained high for ~6 hours and were still detectable at 20 hours, but not at 48 hours. Levels of the metabolite rose during the first 20 hours after high exposure, but at 48 hours the metabolite was no longer detectable. Dimethylformamide and its metabolite monomethylformamide, although rapidly and widely distributed, showed no tendency to accumulate in the tissues examined.

Radioactivity was widely distributed in male Sprague-Dawley rats following an intraperitoneal dose (1 mL/kg) of dimethyl-^{14}C-formamide (Scailteur and Lauwerys, 1984a). At 24 hours, the blood contained ~4% of the dose. Levels in the brain, heart, lungs, stomach, intestines, kidneys and spleen each contained 0.08-0.83% of the dose, while liver, adipose tissue and muscles contained 1.01, 1.12 and 3.07% of the dose, respectively.

4.3. METABOLISM

Numerous investigators (Lyle et al., 1979; Kimmerle and Eben, 1975a,b; Maxfield et al., 1975; Krivanek et al., 1977; Lauwerys et al., 1980; Yonemoto and Suzuki, 1980; Maham, 1977; Sanotskii et al., 1978; Barnes and Ranta, 1972) have detected monomethylformamide and formamide in the urine of humans, dogs or rats exposed to dimethylformamide; until very recently, it was thought that these compounds were formed by successive demethylation catalyzed by microsomal enzymes.

Barnes and Ranta (1972) found that more formaldehyde was liberated when dimethylformamide was incubated with liver homogenates from phenobarbital induced rats than from control rats. They interpreted these findings to suggest that induction of N-demethylase had occurred, and concluded that the metabolism of dimethylformamide was primarily by demethylation. Dahl and Hadley (1983), however, found essentially no formation of formaldehyde (<70 pmol/mg microsomal protein/min) by rat liver or rat nasal microsomal enzymes

incubated with dimethylformamide. Elovaara et al. (1983) also found that incubation of dimethylformamide with rat liver microsomes did not result in liberation of formaldehyde, whereas formaldehyde readily formed when dimethylnitrosamine was used as a substrate. Furthermore, Scailteur et al. (1984) failed to detect formaldehyde or any other one-carbon compound (formic acid, methanol, carbon monoxide or methane) following incubation of dimethylformamide under a variety of conditions with whole homogenates of liver, kidney, lung, brain, intestine or heart, with rat liver, nuclear, mitochondrial, microsomal or supernatant fractions or when cofactors, pH, time of incubation, etc., were varied.

Recent evidence (Brindley et al., 1983; Scailteur and Lauwerys, 1984a,b; Scailteur et al., 1984) suggests that hydroxylation rather than demethylation is the major mechanism for biotransformation of dimethylformamide. Following treatment with an intraperitoneal dose of 6.8 or 19.2 mmol/kg of dimethyl-^{14}C-formamide, blood levels of dimethylformamide in male CBA/CA mice declined, while the level of a metabolite rose and then declined in parallel with dimethylformamide from 9-12 hours after injection (Brindley et al., 1983). The metabolite was identified by GC as monomethylformamide, but may have been N-methyl-N-hydroxymethylformamide, which is known to degrade to monomethylformamide and formaldehyde on GC columns. When the urine from the treated mice was subjected to alkaline hydrolysis, formaldehyde was liberated. The authors stated that formaldehyde is liberated from authentic N-methyl-N-hydroxymethylformamide only upon alkaline hydrolysis, but they could not verify the identity of the metabolite.

Scailteur et al. (1984) and Scailteur and Lauwerys (1984a,b) have studied extensively the in vivo and in vitro metabolism of dimethylformamide by rats. Incubation of dimethylformamide with rat liver microsomes and

cofactors produced a metabolite identified by GC as monomethylformamide (Scailteur et al., 1984). Since no metabolite containing a single carbon atom was found, however, it was suggested that dimethylformamide was metabolized to N-methyl-N-hydroxymethylformamide, which degraded to monomethylformamide during GC analysis. Alkaline hydrolysis of the in vitro products resulted in amounts of formaldehyde stoichiometrically equivalent to the amount of monomethylformamide detected by GC. Analysis by mass spectrometry of urine collected over 24 hours after intraperitoneal dosing of Sprague-Dawley rats identified the metabolites as N-methyl-N-hydroxymethylformamide (~50% of the dose) and N-hydroxymethylformamide (~5% of the dose), rather than monomethylformamide and formamide, respectively.

Scailteur and Lauwerys (1984b) tested the hypothesis that metabolism of dimethylformamide to N-methyl-N-hydroxymethylformamide involves attack by hydroxyl radicals (•OH). Pretreatment or concurrent treatment of rats with •OH scavengers and dimethylformamide, or in vitro incubation of dimethylformamide with the scavengers, decreased or completely inhibited the production of N-methyl-N-hydroxymethylformamide. The degree of inhibition was proportional to the concentration or dose of the scavenger. Stimulation of •OH production by iron-EDTA enhanced the production of N-methyl-N-hydroxymethylformamide in vitro only slightly, but monomethylformamide and formic acid production was increased. When monomethylformamide or N-methyl-N-hydroxymethylformamide was used as a substrate, no formic acid or formaldehyde was formed, suggesting that monomethylformamide and formic acid were not products of N-methyl-N-hydroxymethylformamide metabolism but rather arose from a parallel pathway. Scailteur and Lauwerys (1984a) provided evidence that monomethylformamide, identified by mass spectrometry, is also excreted in the urine of rats treated with dimethylformamide, and is not

merely an artifact of GC analysis. About 4% of the administered dose of radioactivity was identified in the urine of rats treated with dimethyl-^{14}C-formamide as monomethylformamide by mass spectrometry. None was detected in the urine of rats treated with N-methyl-N-hydroxymethylformamide, however, supporting the hypothesis that N-methyl-N-hydroxymethylformamide and monomethylformamide arise from parallel pathways.

Scailteur et al. (1984) found little difference in the amount of N-methyl-N-hydroxymethylformamide and N-hydroxymethylformamide excreted by male and female rats on the first 2 days of intraperitoneal treatment with dimethylformamide at 1.0 mL/kg/day for 4 days compared with 0.5 mL/kg/day. This suggested saturation or inhibition of hydroxylation of dimethylformamide at doses >0.5 mL/kg.

In further experiments, Scailteur et al. (1984) found that pretreatment of male rats with phenobarbital, an inducer of microsomal enzymes, before intraperitoneal injection of dimethylformamide at 1 mL/kg/day for 4 days resulted in significantly less urinary excretion of unchanged dimethylformamide and more excretion of N-methyl-N-hydroxymethylformamide than in rats similarly treated with dimethylformamide, but without phenobarbital pretreatment. These differences occurred during the first 2 days of treatment with dimethylformamide. Thereafter, the excretion of N-methyl-N-hydroxymethyl formamide was significantly less in the urine of pretreated rats than in control rats. Pretreatment of male rats with cobaltous chloride, an inhibitor of microsomal enzymes, resulted in delayed formation of N-methyl-N-hydroxymethylformamide and decreased urinary excretion of N-hydroxymethylformamide. Cobaltous chloride pretreatment of female rats produced a response similar to that in males. In phenobarbital-pretreated female rats, excretion of unchanged dimethylformamide was markedly reduced, but there was

little quantitative effect on the excretion of the metabolites. This implied that phenobarbital may have induced metabolic pathways that are different in females than they are in male rats. Scailteur et al. (1984) suggested that quantitatively different metabolic pathways may operate in male than in female rats. Because female rats excreted greater amounts of unchanged dimethylformamide than males, phenobarbital had little effect on the excretion of metabolites by female rats. Dimethylformamide was less toxic to females than males because the metabolites of dimethylformamide (N-methyl-N-hydroxymethylformamide and N-methylformamide) are substantially more toxic than the parent compound (Scailteur and Lauwerys, 1984a).

The evidence suggests that dimethylformamide is hydroxylated by liver enzymes to N-methyl-N-hydroxymethylformamide, a minor amount of which may undergo demethylation to N-hydroxymethylformamide. These metabolites, as well as unchanged dimethylformamide, are excreted in the urine. At high doses, inhibition of the hydroxylation reaction by N-methyl-N-hydroxymethylformamide appears to occur, which may result in delayed toxicity of dimethylformamide at high exposures. Alternate minor pathways may exist, whereby dimethylformamide is demethylated to monomethylformamide and formic acid, and altogether different pathways may operate in female rats (Scailteur et al., 1984; Scailteur and Lauwerys, 1984a).

4.4. EXCRETION

As the previously described study in mice by Brindley et al. (1983) stated, 82.8±4.7% of the radioactivity from an intraperitoneal dose of 6.8 mmol/kg of dimethyl-^{14}C-formamide was detected in the urine collected over 24 hours. Little additional excretion was detected during the next 48 hours. Of the administered radioactivity, >50% was detected in the urine as N-methyl-N-hydroxymethylformamide and 4.9±1.4% was unchanged dimethylformamide. N-hydroxymethylformamide accounted for 3.4±0.9% of the dose.

Similar results were obtained in rats treated intraperitoneally with 1 mL/kg of dimethyl-^{14}C-formamide (Scailteur and Lauwerys, 1984a). Within 48 hours, total urinary excretion of radioactivity was ~85%; at 72 hours, ~90% of the dose was excreted. N-methyl-N-hydroxymethylformamide, unchanged dimethylformamide and N-hydroxymethylformamide accounted for ~50, 15 and 5% of the administered radioactivity, respectively.

5. EFFECTS

5.1. CARCINOGENICITY

Testing of dimethylformamide for carcinogenicity by the National Toxicology Program has been deferred (NTP, 1985). As reviewed by ACGIH (1980), Druckrey et al. (1967) administered dimethylformamide to rats at oral doses of 75-150 mg/kg for 250-500 days (until a total dose of 38 g/kg was reached) or at subcutaneous doses of 200-400 mg/kg/week (until a total dose of 8-20 g/kg was reached). No tumors were produced by either regimen.

Kommineni (1973) treated 18 male and 19 female MRC rats intraperitoneally with dimethylformamide at 0.1 mL/rat/week for 10 weeks. The dimethylformamide-treated rats served as solvent controls for rats treated with aflatoxin dissolved in dimethylformamide. An untreated control group consisted of 14 male and 14 female rats. The incidence of tumors in the untreated control group was reported to be consistent with "earlier reported results," but specific tumor incidence data were not provided. In the dimethylformamide-treated group, 9/18 males developed 13 tumors (4 pheochromocytomas of the adrenal medulla, 1 stomach sarcoma, 1 colon sarcoma, 1 embryonal cell carcinoma of the testis and 6 benign tumors in unspecified organs), and 11/19 females developed 17 tumors (9 malignant and 8 benign). The tumors observed in females were 2 adenocarcinomas and a leiomyoma of the colon, 1 squamous cell carcinoma of the rectum, 1 adenocarcinoma each of the adrenal cortex and pancreas and 11 tumors of unspecified type in the reproductive organs. Because the incidence of tumors in untreated controls was not provided, it is not possible to evaluate the incidence in the treated rats.

5.2. Mutagenicity

Dimethylformamide has been tested extensively in mutagenicity and genotoxicity assays (Table 5-1). Results for reverse mutation in the bacteria, Salmonella typhimurium, (Richold and Jones, 1981; Nagao and Takahashi, 1981; Ichinotsubo et al., 1981a; MacDonald, 1981; Garner et al., 1981; Martire et al., 1981; Brooks and Dean, 1981; Baker and Bonin, 1981; Hubbard et al., 1981; Venitt and Crofton-Sleigh, 1981; Trueman, 1981; Simmon and Shepherd, 1981; Rowland and Severn, 1981; Gatehouse, 1981; Antoine et al., 1983) and Escherichia coli, (Venitt and Crofton-Sleigh, 1981; Gatehouse, 1981, Matsushima et al., 1981), and in the yeast, Saccharomyces cerevisiae, (Mehta and von Borstel, 1981) were negative in the presence and absence of metabolic activation. Trueman (1981), however, obtained positive results in S. typhimurium strains TA1538 and TA98 in the presence of S-9, but considered the results to be false positive. An abstract of a Czechoslovakian study (Dobias et al., 1981) reported a positive result for reverse mutation in S. typhimurium strains TA98 and TA1538 in a host-mediated assay.

Dimethylformamide was negative for forward mutation in S. typhimurium strain TM677 (Skopek et al., 1981), E. coli 343/113/uvrB (Mohn et al., 1981), Schizosaccharomyces pombe (Loprieno, 1981), human lung fibroblasts (Gupta and Goldstein, 1981) and mouse lymphoma cells (Jotz and Mitchell, 1981) with and without metabolic activation. Negative results were also obtained in most tests for differential toxicity (rec assays) using repair proficient and repair deficient strains of Bacillus subtilis (Kada, 1981), E. coli (Ichinotsubo et al., 1981b; Green, 1981; Rosenkranz et al., 1981; McCarroll et al., 1981), S. cerevisiae (Kassinova et al., 1981) and Chinese hamster ovary cells (Hoy et al., 1984). Sharp and Parry (1981a), however,

TABLE 5-1

Mutagenicity and Genotoxicity Testing of Dimethylformamide

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	plate incorporation	0.65×10^{-5} to 1.3×10^{-5} mol/plate	±S-9	=	Negative in all strains	Antoine et al., 1983
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	plate incorporation	10-10,000 µg/plate	±S-9	=	Negative in all strains	Richold and Jones, 1981
Reverse mutation	S. typhimurium TA1537, TA98, TA100	liquid preincubation	NR	±S-9	=	Also negative in the presence of norharman	Nagao and Takahashi, 1981
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	NR	±S-9	=	NC	Ichinotsubo et al., 1981a
Reverse mutation	S. typhimurium TA100, TA98 TA1537	plate incorporation	≤10,000 µg/plate	±S-9	=	NC	MacDonald, 1981
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	plate incorporation	NR	±S-9	=	NC	Garner et al., 1981
Reverse mutation	S. typhimurium TA100, TA98	plate incorporation	NR	±S-9	=	NC	Martire et al., 1981
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA100, TA98, TA92	liquid preincubation	0.2-2000 µg/plate	±S-9	=	NC	Brooks and Dean, 1981
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA100, TA98	plate incorporation	NR	±S-9	=	NC	Baker and Bonim, 1981
Reverse mutation	S. typhimurium TA98, TA100	fluctuation test	≤500 µg/mL	±S-9	=	Also tested with and without hepatocytes with equivocal results. Dimethylformamide was toxic to the hepatocytes; the release of histidine into the incubation medium may have influenced the results.	Hubbard et al., 1981

TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	0-500 µg/plate	±S-9	=	NC	Venitt and Crofton-Sleigh, 1981
Reverse mutation	S. typhimurium TA1535	plate incorporation	0-2500 µg/plate	±S-9	-	Unequivocal positive response in TA1538 and TA98 considered false positive; the investigator suggested that anomalous result is due to differences in S-9 mix.	Trueman, 1981
	TA1537			±S-9	-		
	TA1538			±S-9	+		
	TA98			±S-9	+		
	TA100			±S-9	-		
Reverse mutation	S. typhimurium TA1535, TA1537 TA1538, TA98, TA100	plate incorporation	NR	±S-9	=	Negative in all strains	Simmons and Shepherd, 1981
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA100, TA98	plate incorporation	0.1-2000 µg/plate	±S-9	=	NC	Rowland and Severn, 1981
Reverse mutation	S. typhimurium TA98, TA1535, TA1537	microtiter fluctuation	10-1000 µg/mL	±S-9	=	NC	Gatehouse, 1981
Reverse mutation (host-mediated)	S. typhimurium TA98, TA1538	intraperitoneal in mice	4.25 or 5.1 mg/kg	NA	+	Mutation rate reached maximum 1 hour after injection and returned to background at 24 hours.	Doblas et al., 1981
Reverse mutation	Escherichia coli WP2, WP2uvrA	plate incorporation	0-500 µg/plate	±S-9	=	NC	Venitt and Crofton-Sleigh, 1981
Reverse mutation	E. coli WP2uvrA	microtiter fluctuation	10-500 µg/mL	±S-9	=	NC	Gatehouse, 1981
Reverse mutation	E. coli WP2	liquid preincubation	NR	±S-9	=	NC	Matsushima et al., 1981
Reverse mutation	Saccharomyces cerevisiae XV185-14C	cell suspension	88.9-889 µg/mL	±S-9	=	NC	Mehta and von Borstel, 1981
Forward mutation	S. typhimurium TM677	liquid preincubation	≤1000 µg/mL	±S-9	-	NC	Skopek et al., 1981

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TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Forward mutation	E. coli 343/113/uvrB	liquid suspension	0-4 mg/mL	±S-9	=	NC	Mohn et al., 1981
Forward mutation	Schizosaccharomyces pompe	cell suspension	0-20 µg/mL	±S-9	=	NC	Loprieno, 1981
Forward mutation	human lung fibroblasts (HSC172)	cell culture	0, 0.2 and 0.5 mg/mL	±S-9	=	NC	Gupta and Goldstein, 1981
Forward mutation	mouse lymphoma cells (L51784)	cell culture	46.9-3000 µg/mL	±S-9	=	NC	Jotz and Mitchell, 1981
Rec assay	Bacillus subtilis H17 (rec+) M45 (rec-)	spot test	≤20 µL/disk	±S-9	=	NC	Kada, 1981
Rec assay	E. coli WP2, WP67 (uvrA, polA), CM871 (uvrA, lexA, recA)	spot test	250-1000 µg/mL	±S-9	=	NC	Tweats, 1981
Rec assay	E. coli 2921, 8239, 8471, 5519, 7632, 7689	spot test	NR	±S-9	=	NC	Ichinotsubo et al., 1981b
Rec assay	E. coli WP2, WP67 (uvrA, polA) CM871 (uvrA, lexA, recA)	liquid preincubation	0-2500 µg/mL	±S-9	=	NC	Green, 1981
Rec assay	E. coli W3110 (polA+) p3478 (polA-)	liquid preincubation	NR	±S-9	=	NC	Rosenkranz et al., 1981
Rec assay	E. coli WP2, WP2uvrA, WP67, CM611, WP100, W3110 polA+, P3478 pol-	microsuspension	2x10⁴ µg/well	±S-9	=	NC	McCarroll et al., 1981

TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Rec assay	S. cerevisiae 197/2d (repair proficient) rad (repair deficient)	liquid preincubation	0-750 µg/mL	±S-9	‡	Positive at ≥500 µg/mL, considered to be false positive	Sharp and Parry, 1981a
Rec assay	S. cerevisiae T_4 and T_5	spot test	100 µg/mL	±S-9	=	NC	Kassinova et al., 1981
Rec assay	Chinese hamster cells: repair deficient and wild type AA8	cell incubation	8.0 µL/mL	±S-9	=	NC	Hoy et al., 1984
				± microsomal pellet	=		
Lambda induction	E. coli C600	liquid preincubation	20 µL/mL	+S-9	-	NC	Thomson, 1981
Sex-linked recessive lethal	Drosophila melanogaster	adult feeding	0.2%	NA	-	NC	Wurgler and Graf, 1981
Mitotic gene conversion	S. cerevisiae JD_1	liquid incubation	0-100 µg/mL	±S-9	=	NC	Sharp and Parry, 1981b
Mitotic gene conversion	S. cerevisiae D7	liquid cell suspension	5 µL/mL	±S-9	=	NC	Zimmerman and Scheel, 1981
Mitotic gene conversion	S. cerevisiae D4	plate incorporation	0.33-333.33 µg/plate	±S-9	=	NC	Jagannath et al., 1981
Mitotic cross-over	S. cerevisiae T1 and T2	cell suspension	1000 µg/mL	±S-9	=	NC	Kassinova et al., 1981
Mitotic aneuploidy	S. cerevisiae D6	cell suspension	0-100 µg/mL	±S-9	‡	Positive at >25 µg/mL, considered to be false positive	Parry and Sharp, 1981
UDS	rat hepatocytes	cell culture	10^{-8} M	NA	-	NC	Ito, 1982
UDS	rat hepatocytes	cell culture	10^{-9} M	NA	-	NC	Williams, 1977
UDS	mouse hepatocytes	cell culture	3 concentrations, not otherwise specified	NA	-	NC	Klaunig et al., 1984
UDS	mouse or hepatocytes	cell culture	10^{-9} M	NA	-	Negative for both species	McQueen et al., 1983

TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
UDS	HeLA cells	cell culture	NR	±S-9	=	NC	Martin and McDermid, 1981
UDS	human fibroblasts	cell culture	NR	±S-9	=	NC	Agrelo and Amos, 1981a
UDS	human fibroblasts WI-38 cells	cell culture	1.1-90 µg/mL	±S-9	=	NC	Robinson and Mitchell, 1981
SCE	Chinese hamster ovary cells	cell culture	0.1-100 µg/mL	±S-9	=	NC	Perry and Thomson, 1981
SCE	Chinese hamster ovary cells	cell culture	<6.67 µg/mL	±S-9	=	NC	Natarajan and van Kesteren-van Leeuwen, 1981
SCE	Chinese hamster ovary cells	cell culture	0.00625-0.1%	±S-9	=	NC	Evans and Mitchell, 1981
SCE	mouse bone marrow and liver cells	intraperitoneal injection of mice	60-80% LD_{50}	NA	-	NC	Paika et al., 1981
SCE	human lymphocytes	cell culture	$1.1x10^{-9}$ to 1.1 M	none	-	NC	Antoine et al., 1983
Chromosome aberrations	rat hepatocytes	cell culture	75-300 µg/mL	NA	-	NC	Bean, 1981
Chromosome aberrations	mouse bone marrow cells	intraperitoneal injection of mice	10^{-6} to 10^{-8} mol/mice	NA	+	Dose-related increase in breaks	Doblas et al., 1981
Chromosome aberrations	human lymphocytes	cell culture	$1.1x10^{-9}$ to 1.1 M	none	-	NC	Antoine et al., 1983
Chromosome aberrations	human lymphocytes	cell culture	10^{-9} to 10^{-7} M	none	+	Incubated for 3 days	Doblas et al., 1981
Chromosome aberrations	human lymphocytes	occupational exposure 4-6 months	NR	NA	+	2.74-3.82% compared with 1.10-1.61% in controls	Koudela and Spazier, 1981

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TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Micronucleus test	mouse bone marrow cells	intraperitoneal injection of mice	50 or 80 µg/mouse	NA	-	NC	Salamone et al., 1981
Micronucleus test	mouse bone marrow cells	intraperitoneal injection of mice	2x2.72 mL/kg	NA	-	NC	Katz et al., 1981
Micronucleus test	BALB/c mouse bone marrow cells	intraperitoneal injection of mice	0.2, 20 or 2000	NA	-	NC	Antoine et al., 1983
Abnormal sperm	mouse	intraperitoneal injection of mice	0.1-1.5 mg/kg/day for 5 days	NA	-	NC	Topham, 1981
Abnormal sperm	BALB/c mouse	intraperitoneal injection of mice	0.2, 6.6, 20, 66.6, 200, 666.6 or 2000 mg/kg	NA	-	NC	Antoine et al., 1983
Nuclear enlargement	HeLa cells	cell culture	8-200 µg/mL	+S-9	+	NC	Agrelo and Amos, 1981b
Nuclear enlargement	human fibroblasts	cell culture	8-200 µg/mL	+S-9	-	NC	Agrelo and Amos, 1981b
Cell transformation	baby hamster kidney cells	cell culture	NR	+S-9	-	NC	Styles, 1981
Cell transformation	baby hamster kidney cells	cell culture	NR	±S-9	‡	Results surprising to the investigators	Daniel and Dohnel, 1981

NR = Not reported; NA = not applicable; NC = no comment

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reported that dimethylformamide was positive for differential toxicity in S. cerevisiae in the presence and absence of S-9, but considered the results to be false positive.

Dimethylformamide treatment of a lysogenic strain of E. coli carrying prophage lambda did not result in the induction of the prophage in the presence of metabolic activation (Thomson, 1981). A negative result was also obtained in the sex-linked recessive lethal assay in Drosophila melanogaster (Wurgler and Graf, 1981). Dimethylformamide was also negative with and without metabolic activation in mitotic gene conversion and mitotic crossover tests in S. cerevisiae (Sharp and Parry, 1981b; Zimmerman and Scheel, 1981; Jagannath et al., 1981; Kassinova et al., 1981); however, Parry and Sharp (1981) reported that dimethylformamide treatment of S. cerevisiae resulted in a false positive response for mitotic aneuploidy.

Tests for UDS and SCE in mammalian cells were negative (Ito, 1982; Williams, 1977; Klaunig et al., 1984; McQueen et al., 1983; Martin and McDermid, 1981; Agrelo and Amos, 1981a; Robinson and Mitchell, 1981; Perry and Thomson, 1981; Natarajan and van Kesteren-van Leeuwen, 1981; Evans and Mitchell, 1981; Paika et al., 1981; Antoine et al., 1983). Equivocal results were obtained in chromosome aberration assays. Dean (1981) and Antoine et al. (1983) reported that dimethylformamide did not induce chromosome damage in rat hepatocytes and human lymphocytes, while positive results in mouse bone marrow cells and human lymphocytes were reported in an abstract of a Czechoslovakian study (Dobias et al., 1981). Another abstract of a Czechoslovakian study (Koudela and Spazier, 1981) reported that workers exposed occupationally to dimethylformamide had an increased incidence of chromosome aberrations in lymphocytes compared with nonexposed controls.

Intraperitoneal injection of mice with dimethylformamide resulted in negative responses in the micronucleus test and the abnormal sperm test (Salamone et al., 1981; Katz et al., 1981; Antoine et al., 1983; Topham, 1981).

In the presence of S-9, dimethylformamide resulted in nuclear enlargement in HeLa cells, but not in human fibroblasts (Agrelo and Amos, 1981b). Negative results of cell transformation assays in baby hamster kidney cells were reported by Styles (1981), but positive results were reported by Daniel and Dehnel (1981); neither of these studies reported the dose of dimethylformamide used in the assay.

Therefore, with the exception of a few false positive tests, the overwhelming evidence indicates that dimethylformamide is not mutagenic or genotoxic.

5.3. TERATOGENICITY

The teratogenicity of dimethylformamide has been investigated in a number of species using oral, inhalation, dermal and intraperitoneal routes of exposure.

Merkle and Zeller (1980) treated groups of 11-18 female Russian rabbits by gavage with dimethylformamide on days 6-18 postinsemination. The dams were killed on day 28 post insemination. The doses were 0, 46.4, 68.1 and 200 µl/kg/day. Using the density of dimethylformamide at 25°C of 0.9445 g/ml or 0.9445 mg/µl (see Section 1.2.), the doses are equal to 0, 43.8, 64.3 and 188.9 mg/kg/day. The highest dose was toxic to the dams, resulting in decreased food intake and weight gain. As seen in Table 5-2, the number of implantations/dam and the number of live fetuses/dam in the mid-dose group were significantly ($p \leq 0.01$) lower than control; however, no significant differences in these parameters were observed in the high-dose group.

TABLE 5-2

Teratogenicity and Fetoxicity of Dimethylformamide Administered by Gavage to Pregnant Rabbits[a]

Parameter	Dose Group			
	Control	46.4 µL/kg/day	68.1 µL/kg/day	200 µL/kg/day
Number of pregnant rabbits/number in group	22/24	10/12	16/18	11/11
Number of abortions	1	0	0	3
Corpora lutea/dam (±SD)	8.3±1.53	9.2±1.62	8.3±2.15	8.8±2.60
Implantations/dam (±SD)	7.0±2.12	5.0±3.02	4.9±2.05[b]	6.4±2.13
Live fetuses/dam (±SD)	6.3±2.11	4.6±3.03	3.9±2.03[b]	5.6±1.85
Total dead fetuses	0	0	0	0
% Resorptions/dam	9.2	10.0	17.5	10.7
Mean fetal weight in g (±SD)	36.3±3.19	35.3±3.77	36.0±4.97	29.7±5.18[b]
Total number of runts	1	0	0	0
Number of fetuses with malformations (% of live fetuses/litter)	0 (0)	1 (1.1)	3 (3.6)	16 (33.3[b])

TABLE 5-2 (cont.)

Parameter	Dose Group			
	Control	46.4 µl/kg/day	68.1 µl/kg/day	200 µl/kg/day
Number of litters with malformed fetuses (%)	0 (0)	1 (10)	2 (13.3)	7 (87.5[b])
Number of fetuses with variations and retarded development (% of live fetuses/litter)	49 (38.5)	14 (34.1)	28 (46.4)	33 (68.0)

[a]Source: Merkle and Zeller, 1980

[b]$p \leq 0.01$

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A statistically significant decreased mean fetal weight was observed at the high dose compared with control. There were statistically significant increases in the percentage of malformed live fetuses/litter and the percentage of litters with malformed fetuses in the high-dose group compared with controls. A few malformed fetuses were observed at the lower doses: one fetus with hydrocephalus at 46.4 µL/kg/day and three fetuses with hydrocephalus at 68.1 µL/kg/day. At the high dose, there were six fetuses with hydrocephalus, one fetus with abnormal position of extremities, two with exophthalmos, three with simple eventration, seven with umbilical hernia, and one with cleft palate. Therefore, the high dose was teratogenic, fetotoxic and maternotoxic in rabbits.

In an inhalation study, reported in abstract form, groups of 19 pregnant Sprague-Dawley rats were exposed to dimethylformamide at concentrations of 0, 32 or 301 ppm (0, 96 or 900 mg/m³), 6 hours/day on days 6-15 of gestation (Keller and Lewis, 1981). The dams were killed on day 21 of gestation. At 32 ppm, no effects on fetal survival, fetal size, or the incidence of soft tissue or skeletal variations were observed; however, there was a slight, but statistically significant ($p<0.05$) reduction in implantation efficiency (87.3% vs. 92.5% of control). At 301 ppm, dams had reduced weight gain during the exposure period, and there was a slight (5.3 vs. 5.5 g in controls) but significant ($p<0.05$) decrease in mean fetal weight. The incidence of ossification variations at 301 ppm (75.0%) was significantly increased ($p<0.01$) compared with controls (60.2%).

Kimmerle and Machemer (1975) observed no signs of maternal toxicity in groups of 22 or 23 female rats exposed by inhalation to dimethylformamide at 18 or 172 ppm (54 or 514 mg/m³), 6 hours/day on days 6-15 of gestation.

No fetal malformations were observed; however, at 172 ppm, fetal weight was significantly decreased compared with controls. Additional details were not provided in the review by U.S. EPA (1981).

As reported in abstracts of Russian studies (Sheveleva and Osina, 1973; Sheveleva et al., 1979), an unspecified number of pregnant rats exposed to 10.7, 50 or 600 mg/m³, 4 hours/day for 20 gestational days had increased embryonic mortality at all exposure levels and decreased fetal growth at 50 and 600 mg/m³. Sheveleva and Osina (1973) also reported functional CNS and liver changes, and altered blood composition of rat pups at unspecified exposure levels.

U.S. EPA (1981) reviewed a Russian study (Gofmekler et al., 1970) in which pregnant rats were exposed to 0.01-500 mg/m³ of dimethylformamide throughout the gestational period. It was not clear if the exposure was continuous. At the highest exposure level, all dams aborted and 5/12 dams died. Mean number of fetuses/litter showed no consistent dose-related trend. High exposures (not otherwise specified) resulted in microscopic structural changes in the fetuses. Additional pertinent details were not provided in the review.

Stula and Krauss (1977) studied the teratogenicity of undiluted dimethylformamide applied dermally to the shaved backs of pregnant Sprague-Dawley rats and New Zealand White rabbits on various days of gestation. Day 1 of gestation was defined as the day on which sperm-positive vaginal smears were observed. The rats and rabbits were killed on days 20 and 30 of gestation, respectively. The dosing schedule and results are presented in Table 5-3. For rats, significantly increased embryomortality (resorption sites plus dead fetuses), defined as >10% of the implantation sites, based on historical control data, was observed only at doses that were lethal to dams

TABLE 5-3

Embryotoxic Effects of Dimethylformamide Applied to Skin of Pregnant Rats and Rabbits[a]

Number of Pregnant Animals in Group		Daily Dose (mg/kg)	Gestation Days Applied	48-Hour Maternal Body Weight Change (%)	Embryomortality (%)	Average Fetal Weight (g)	Fetal Abnormalities
Rats:	6	H_2O control	11+12	+4	3	2.7	0
	7	600	9	NM	3	2.7	0
	3	600	10+11	0	2	2.5	0
	6	600	11+12	+2	4	2.9	0
	8	600	12+13	0	4	2.5	0
Rats:	6	H_2O control	10+11	+4	3	2.3	0
	6	600	10+11	+2	8	2.5	0
	8	1200	10+11	+2	4	2.6	0
	7	2400	10+11	0	26[b]	2.4	0
Rats:	6	H_2O control	10+11	+3	9	2.1	0
	9	2400	10+11	0	9	2.2	0
Rats:	8	H_2O control	12+13	+4	1	2.5	0
	8	600	12+13	+4	5	2.4	9/84: subcutaneous hemorrhage
	7	1200	12+13	+2	4	2.5	5/73: subcutaneous hemorrhage
	8	2400	12+13	+2	4	2.4	4/83: subcutaneous hemorrhage
Rats:	4	0 Control	NA	+3	4	2.3	0
	7[c]	200x6	11+12+13	0	43	2.2	3/40: subcutaneous hemorrhage
	8[d]	400x6	11+12+13	-2	30	1.9	0
Rabbits:	4	H_2O control	8-16	NM	3	28.4	0
	5	200	8-16	NM	6	32.9	0

[a]Source: Stula and Krauss, 1977

[b]8/14 resorptions in one dam

[c]Not included were three rats that died.

[d]Not included was one rat that died.

NA = Not applicable; NM = not measured

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(6x200 or 6x400 mg/kg/day). The incidence of subcutaneous hemorrhage in rat fetuses (see Table 5-3) was not different from historical control incidences and were, therefore, considered to be unrelated to treatment. No embryotoxicity or maternal toxicity was observed in rabbits treated dermally at 200 mg/kg/day on days 8-16 of gestation (see Table 5-3).

The U.S. EPA (1981) reviewed several studies from the German literature of dimethylformamide administered intraperitoneally to pregnant rodents. Thiersch (1971) found no treatment-related effects on fetuses following intraperitoneal treatment of an unspecified number of pregnant rats with 0.5-2 mL/kg dimethylformamide (472-1889 mg/kg, based on the density of dimethylformamide as given in Section 1.2.) on day 7 or 11 of gestation. A single intraperitoneal dose of dimethylformamide administered at an unspecified time to pregnant mice resulted in embryotoxicity (Scheufler and Freye, 1975). Scheufler (1976) found a 75% fetal malformation rate following repeated intraperitoneal injections of pregnant mice with unspecified doses of dimethylformamide over 10 or 14 days of gestation. Dimethylformamide was not teratogenic to the offspring of pregnant NMRI mice treated intraperitoneally with 1.24 mL/kg (1171 mg/kg) on days 6-15 of gestation (Gleich, 1974). Schmidt (1976) found dose-related embryotoxicity and teratogenic effects in the offspring of mice treated with an unspecified dose by an unspecified route on days 3, 7, 9 or 11 of gestation. Additional details of these studies were not provided in the review (U.S. EPA, 1981).

5.4. OTHER REPRODUCTIVE EFFECTS

Dilution of human semen with dimethylformamide at 2.5-10.0% resulted in significant ($p<0.01$) concentration-related increases in the loss of sperm motility and mean progression ratings (Richardson and Sadleir, 1967).

Farquharson et al. (1983) reported three unexplained cases of intrauterine death in the third trimester in women employed by a pharmaceutical laboratory. These cases represented a 30% stillbirth rate for women in the laboratory compared with 0.26% for the general population in the geographic area. The laboratory workers had been exposed to dimethylformamide among a variety of other chemicals. An abstract of a Russian study (Schottek, 1972), reported that pregnant women exposed for unspecified durations to dimethylformamide (100 mg/m³) had a 10-fold increase in the spontaneous abortion rate. As reported in the same abstract (Schottek, 1972), pregnant rats exposed to unspecified concentrations of dimethylformamide had a 5-fold increase in the number of resorptions. Additional details were not provided.

An abstract of another Russian study reported that exposure of male rats by inhalation to dimethylformamide at ≤616 mg/m³ for ≤8 days had no effect on testicular function (Sheveleva et al., 1979).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The only long-term study of dimethylformamide located in the available literature, the carcinogenicity study of Druckrey et al. (1967), was presented previously in Section 5.1.; however, information regarding other effects was not provided. Several subchronic studies were available.

Becci et al. (1983) maintained groups of 30 male and 30 female CD-1 mice on diets containing dimethylformamide at concentrations of 0, 160, 540 and 1850 ppm for 119 days. Based upon food consumption and body weight data, the investigators calculated the mean consumption of dimethylformamide to be 0, 22, 70 and 246 mg/kg/day for male mice and 0, 28, 96 and 326 mg/kg/day for female mice. No treatment-related effects were observed for food consumption, body weight gain, food efficiency, behavior or physical appearance. Results of gross and microscopic ophthalmic examinations were unremarkable.

Although SGPT levels were significantly ($p<0.05$) increased in the high-dose females, hemoglobin concentration was significantly increased in low-dose females and hematocrit values were significantly decreased in high-dose females, the values were within normal ranges for mice. No differences in clinical chemistry or hematological parameters were observed in male mice. Results of urinalysis were comparable among groups. High-dose females had significantly ($p<0.05$) increased absolute and relative weights of the thyroid and adrenal glands. Male and female mice had a significant ($p<0.05$) dose-related increase in absolute and relative liver weights. The increased relative liver weights were significantly different from control for mid-dose females and high-dose males and females. Histologic examination was performed only on high-dose and control animals. Other than a slight hepatocytomegaly in a majority of high-dose males and females, no treatment-related histopathologic effects were observed.

Becci et al. (1983) maintained groups of 25 male and 25 female Wistar rats at dietary levels of dimethylformamide of 0, 215, 750 and 2500 ppm for 104 days. The dietary levels were equivalent to dosages of 0, 18, 61 and 210 mg/kg/day for male rats and 0, 20, 69 and 235 mg/kg/day for female rats. Body weight gain was significantly ($p<0.05$) decreased in high-dose males and females compared with controls, while food consumption was significantly decreased in mid-dose females and high-dose males and females. No significant effect, however, was observed on food efficiency. Although clinical chemistry, urinalyses and hematological parameters were within normal ranges for rats, low-dose males had significantly reduced hematocrit values and high-dose males had significantly increased sodium levels compared with controls. No ocular effects were observed. High-dose males had significantly increased relative, but not absolute, weights of brain and testes.

Dose-related increases in absolute liver weight of females and relative liver weight of males and females were observed; the difference compared with control was significant for mid-dose females and high-dose males and females. Comprehensive histological examination performed on high-dose and control groups revealed no treatment-related effects.

As reviewed by Llewellyn et al. (1974) and U.S. EPA (1981), Du Pont (1968) and E.I. Du Pont de Nemours and Company, Inc. (1980) reported that in male and female rats fed diets containing 200, 1000 and 5000 ppm dimethylformamide for 90 days, slight liver damage, slight anemia, leukocytosis and hypercholesterolemia were observed in rats treated at 5000 ppm. Additional details were not provided.

In a subchronic study by Savolainen (1981), groups of 10 male Wistar rats were exposed to dimethylformamide in the drinking water at concentrations of 0, 1.4, 6.8 or 13.7 mmol/ℓ (0, 102.3, 497.0 or 1001 mg/ℓ); five rats/group were killed after 2 and 7 weeks, and determinations of brain enzyme activities were made. Based on body weight and water consumption data, the rats consumed total dosages of dimethylformamide of 0, 1.5, 7.5 and 14.4 mmol/kg (0, 7.8, 47.0 and 75.2 mg/kg/day) after 2 weeks and 0, 4.7, 24.0 and 43.9 mmol/kg (0, 7.0, 35.8 and 65.5 mg/kg/day) after 7 weeks. No effects were observed on body weight gain or behavior. High-dose rats had significantly ($p<0.05$) decreased levels of cerebral glutathione at 2 and 7 weeks. A dose-related decrease in the activity of cerebral succinate dehydrogenase occurred that was significantly lower than control in the middle- and high-dose rats at 2 weeks; the activity remained depressed at 7 weeks. Azoreductase activity was decreased significantly at all dose levels at 7 weeks, while RNA content of the cerebrum was increased significantly at the high dose after 7 weeks. Biochemical changes in the glial cells included

significantly increased acid proteinase in the high-dose group at 2 and 7 weeks, significantly dose-related increased activity of 2',3'-cyclic nucleotide 3'-phosphohydrolase at 2 weeks and significantly decreased glial cell succinate dehydrogenase at all levels after 7 weeks. These biochemical changes were discussed in relation to the inhibitory action of formic acid, a minor metabolite of dimethylformamide (see Section 4.3.), on mitochondrial cytochrome oxidase, and the investigators concluded that dimethylformamide may be toxic to glial cells by inhibiting mitochondrial respiration.

In a similar study of the effects of dimethylformamide on the drug-metabolizing enzymes of the liver and kidney, groups of 10 male Wistar rats received the compound in the drinking water at 0, 100, 500 or 1000 mg/l (Elovaara et al., 1983). Five rats/group were killed after 2 and 7 weeks and livers and kidneys were removed, weighed and homogenized. No effect on body weight gain or kidney weight was observed; however, there was a dose-related significant increase in relative liver weight after 2 weeks, which became more pronounced at 7 weeks. In the liver, no treatment-related effects on cytochrome P-450 content or NADPH-cytochrome c reductase activity occurred, but glutathione levels and 7-ethoxycoumarin o-deethylase activity increased in a time- and dose-related manner. A dramatic dose- and time-related increase in UDP glucuronosyl transferase activity was observed. Although incubation of dimethylformamide with rat liver microsomes did not result in liberation of formaldehyde (see Section 4.3.), there was a significant increase in endogenous formaldehyde liberation by microsomes from rats treated at 1000 mg/l for 7 weeks and significantly decreased activities of formaldehyde and propionaldehyde dehydrogenases at 500 and 1000 mg/l. In the kidneys, glutathione content and deethylase activity increased and

cytosolic formaldehyde dehydrogenase activity decreased. The investigators discussed the findings of altered aldehyde metabolism in relation to the enhancement by dimethylformamide of the toxicity of other chemicals, particularly ethanol (Section 5.6.).

As reported in an abstract of a Russian study by Martinchuk et al. (1984), rats receiving oral doses of dimethylformamide of 200 mg/kg/day for 4 weeks had reduced levels of cytochrome P-450 and reduced demethylase activity in the liver.

Llewellyn et al. (1974) reported that 4/12 female Mongolian gerbils exposed to dimethylformamide in the drinking water at 10,000 mg/ℓ died within 200 days. Based on drinking water consumption data, the mean total dose was >100,000 mg/kg (>500 mg/kg/day). Microscopic examination revealed necrotic lesions in the livers of all the gerbils that died. At 17,000 mg/ℓ, one-half of the gerbils died within 80 days, and the cumulative dose was 90,206 mg/kg (1128 mg/kg/day). At concentrations of 34,000 and 66,000 mg/ℓ, one-half of the gerbils died within 6 and 3 days, respectively. It should be noted that individual water consumption varied widely within groups.

As reported in an abstract of a Russian study, oral administration of dimethylformamide to guinea pigs at 400 mg/kg/day for 14 days resulted in decreased ascorbic acid content of the liver, adrenals and urine (Leshik and Feoktistova, 1984). In the liver, the concentration of dehydroascorbic acid increased and cytochrome P-450 decreased.

The toxicity of inhaled dimethylformamide has been studied in a number of species. As reviewed by ACGIH (1980), Hofmann (1960) found no evidence of liver or kidney damage in cats or rabbits exposed to 300 ppm (897 mg/m^3) for 6 hours/day for 10 months or in rats or cats exposed to 1000

ppm (2989 mg/m³) for unspecified durations for 10 weeks. Clayton et al. (1963), however, reported that exposure of dogs (4 males), rabbits (2/sex), guinea pigs (10 males), rats (10/sex) and mice (11 females) to 23 ppm (69 mg/m³) for 5.5 hours/day, followed by 426 ppm (1273 mg/m³) for 0.5 hours/day, 5 days/week for 58 weekdays resulted in histopathologic effects on the liver, pancreas, spleen, kidneys, adrenals and thymus and functional effects on the liver of all species. In addition, dogs had degenerative changes in the heart and decreased systolic blood pressure. Clayton et al. (1963) also reported significant functional changes in the blood pressure of dogs exposed to 20 ppm (60 mg/m³), 6 hours/day for 107 exposures.

Massmann (1955, 1956) exposed groups of 2 cats and 16 rats to dimethylformamide at concentrations in air of 100, 230 and 450 ppm (299, 688 and 1345 mg/m³), 8 hours/day, 6 days/week for 120 days; no control groups were included in the study. At the highest concentration, 2/2 cats and 6/16 rats died within 56 days, but no deaths occurred in the other exposure groups. No signs of toxicity were observed in rats, but all cats refused food and lost weight. Histological examination of rats and cats revealed necrosis and fatty degeneration of the liver at $\geq$100 ppm.

As reported in abstracts of Italian studies, heart damage was observed in rats exposed to an unspecified concentration of dimethylformamide for 0.5 hours/day for 30 days (Cruz and Maccioni, 1978) and in rabbits exposed to 40 ppm (120 mg/m³), 8 hours/day for 50 days (Arena et al., 1982). Inhalation exposure of rats to unspecified concentrations for 1 hour/day for 15 days or 0.5 hours/day for 30 days resulted in endothelial engorgement and mesangium hypertrophy of the renal glomerulus (Costa et al., 1978).

U.S. EPA (1981) reviewed studies from the Russian literature. Continuous inhalation exposure of white rats to 0.5 or 10 mg/m³ for 2 months resulted in decreased cholinesterase levels (not otherwise specified) and reduced elimination of coproporphyrin by the liver (Odoshashvili, 1963). Exposure of unspecified species to 130 mg/m³ for 4 hours/day for 27 days resulted in decreased blood pressure, while continuous exposure to 130 mg/m³ resulted in increased blood pressure (Germanova et al., 1979).

Effects of occupational exposure to dimethylformamide were described in abstracts of Italian studies. Di Lorenzo and Grazioli (1972) found that 40.7% of 28 exposed workers in an acrylic fiber factory had leukopenia, 82.1% had lymphocytosis and 14.2% had basophilia. Gastroduodenal hyperdyskinesia and gastritis were observed upon gastroscopy. Of 264 exposed workers in a synthetic leather plant, 55.5% had dyspepsia, 37% had diarrhea and 29.6% had alcohol intolerance (Paoletti and Iannaccone, 1982). Exposure levels or durations were not reported in either abstract.

5.6. OTHER RELEVANT INFORMATION

Values for the acute LD_{50} of dimethylformamide are presented in Table 5-4. For adult rats, mice and gerbils, the oral LD_{50} values ranged from ~3-7 g/kg (Bartsch et al., 1976; Massmann, 1956; Kimura et al., 1971; Llewellyn et al., 1974). Dimethylformamide was more toxic to 14-day-old rats than to young adult and older rats; however, the differences in the oral LD_{50} values among the three groups were not statistically significant (Kimura et al., 1971). Kimura et al. (1971) attempted to determine the oral LD_{50} in neonatal rats, but volume limitations precluded accurate determination; the LD_{50} for neonates was approximated to be <1.0 mL/kg (<945 mg/kg). The dermal LD_{50} in rabbits was reported to be 5000 mg/kg (U.S. EPA, 1981). Dimethylformamide was more acutely toxic when administered

TABLE 5-4

Acute LD_{50} Values for Dimethylformamide

Route	Species/Strain	Sex	Age/Weight	LD_{50} (95% Confidence Limits) (ml/kg)	LD_{50} (95% Confidence Limits) (mg/kg)*	Time to Death	Reference
Oral	mouse/NMRI	M,F	NR/15-25 g	6.8 (5.4-8.5)	6443 (5100-8028)	≤24 hours	Bartsch et al., 1976
Oral	rat/ Sprague-Dawley	M,F	NR/170-230 g	7.6 (7.2-8.1)	7178 (6800-7650)	≤24 hours	Bartsch et al., 1976
Oral	rat/albino	NR	NR/180-220 g	3.7	3495	12 hours-12 days	Massmann, 1956
Oral	rat/ Sprague-Dawley	M,F	14 days/16-50 g	1.5 (0.9-2.7)	1417 (850-2550)	NR	Kimura et al., 1971
Oral	rat/ Sprague-Dawley	M	NR/80-160 g	4.2 (2.7-6.6)	3967 (2550-6234)	NR	Kimura et al., 1971
Oral	rat/ Sprague-Dawley	M	NR/300-470 g	7.2 (6.0-8.6)	6800 (5667-8122)	NR	Kimura et al., 1971
Oral	gerbil/ Mongolian	F	NR/50 g	NR	3250	≤24 hours	Llewellyn et al., 1974
Dermal	rabbit/NR	NR	NR	NR	5000	NR	U.S. EPA, 1981
Intraperitoneal	mouse/NMRI	M,F	NR/15-25 g	6.2 (5.4-7.1)	5856 (5100-6706)	≤24 hours	Bartsch et al., 1976
Intraperitoneal	mouse/albino	NR	NR/18-23 g	3.0	2833	NR	Massmann, 1956
Intraperitoneal	rat/ Sprague-Dawley	M,F	NR/170-230 g	4.7 (4.2-5.2)	4439 (3937-4911)	≤24 hours	Bartsch et al., 1976
Intraperitoneal	rat/albino	NR	NR/180-220 g	1.4	1322	6 hours-10 days	Massmann, 1956
Intraperitoneal	rabbit/NR	NR	NR	NR	1000	NR	U.S. EPA, 1981
Intraperitoneal	guinea pig/NR	NR	NR	NR	4000	NR	U.S. EPA, 1981
Intraperitoneal	cat	NR	NR	NR	500	NR	U.S. EPA, 1981
Subcutaneous	rat/albino	NR	NR/180-220 g	3.8	3589	6 hours-6 days	Massmann, 1956

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TABLE 5-4 (cont.)

Route	Species/Strain	Sex	Age/Weight	LD_{50} (95% Confidence Limits) (ml/kg)	LD_{50} (95% Confidence Limits) (mg/kg)*	Time to Death	Reference
Intravenous	mouse/NMRI	M,F	NR/15-25 g	3.7 (3.3-4.2)	3495 (3117-3967)	≤24 hours	Bartsch et al., 1976
Intravenous	rat/ Sprague-Dawley	M,F	NR/170-230 g	3.0 (2.4-3.8)	2834 (2267-3589)	≤24 hours	Bartsch et al., 1976
Intravenous	dog	NR	NR	NR	470	NR	U.S. EPA, 1981

*Where the LD_{50} was given as ml, the dose in mg/kg was calculated using a density of 0.9445 g/ml (see Section 1.2.)

NR = Not reported

intraperitoneally or intravenously to rats and mice than when given orally (Bartsch et al., 1976; Massmann, 1956). Dimethylformamide appears to be somewhat more acutely toxic to cats and dogs than to rodents (see Table 5-4). U.S. EPA (1981) reported a 2-hour inhalation LC_{50} of 3155 ppm (9400 mg/m³) for mice.

Other effects of acute exposure of animals to dimethylformamide are summarized in Table 5-5. The hepatoxicity of dimethylformamide following acute intraperitoneal dosing has been demonstrated in rats, rabbits and cats (Mathew et al., 1980; Lundberg et al., 1981; Massmann, 1956). Dimethylformamide treatment of rodents also resulted in altered metabolism of other xenobiotics, as evidenced by increased pentobarbitol sleeping time of mice (Weetman and Crossfield, 1982) and increased rate of aniline metabolism by microsomes of rats (Stock et al., 1970). Cats treated intraperitoneally or intravenously had abnormal ECGs, hypotension and ventricular fibrillation (Massmann, 1956; Pearl et al., 1978), while dogs treated intravenously had increased myocardial contraction activity (Chanh et al., 1973).

Burges et al. (1969) and Spilker (1970) studied the effect of dimethylformamide on myocardial contractility in vitro. Concentrations of 0.1-3.0% dimethylformamide resulted in a concentration-related increased contractility of excised guinea pig left atria. The maximum increase was 320% (Burges et al., 1969). Dimethylformamide also had a positive dose-related inotropic action on cat left atria, cat papillary muscle, rat left atria, rabbit left atria and dog trabeculae (Spilker, 1970).

Kawalek and Andrews (1980) studied the effect of dimethylformamide on drug metabolism in vitro. At a concentration of 0.70 mmol/mL, dimethylformamide significantly ($p<0.01$) inhibited the metabolism of aniline, aminopyrine and 7-ethoxycoumarin by liver S-9 fractions from Aroclor-pretreated

TABLE 5-5

Effects of Acute Administration of Dimethylformamide

Species	Route	Dose	Duration	Effect	Reference
Rat	intraperitoneal	0.6, 0.9 or 1.2 mL/kg (567, 850 or 1133 mg/kg)	single dose	Dose-related increased severity of liver lesions at ≥0.6 mL/kg, progressing to severe central phlebitis and centrilobular necrosis	Mathew et al., 1980
Rat	intraperitoneal	240 or 479 mg/kg	single dose	Increased serum sorbitol dehydrogenase levels; fatty changes in liver, centrilobular necrosis; the onset of histological changes was delayed after the high dose compared with the low dose	Lundberg et al., 1981
Rat	oral or intraperitoneal	1-40 mL/kg (945-37,780 mg/kg)	single dose	Death at ≥5 mL/kg oral, death at ≥2 mL/kg intraperitoneally, no effect on brain cholinesterase for either case	Weiss and Orzel, 1967
Rat	inhalation	250-600 ppm (747-1794 mg/m³) 4 hours/day	5-10 days	Gastroenteritis, pulmonary edema, increased lung weight, increased mortality	Schottek, 1970
Rat	intraperitoneal	0.5 mL/kg (472 mg/kg)	2 times/day for 3 days	Significantly increased rate of aniline metabolism by microsomes	Stock et al., 1970
Mouse	intraperitoneal	1.15 g/kg (1150 mg/kg)	single dose	Doubled pentobarbital sleeping time	Weelman and Crossfield, 1982
Guinea pig	intraperitoneal	0.5 or 2.0 mL/animal (472 or 1889 mg/animal)	single dose	Death after 6 hours at 2.0 mL, after 48 hours at 0.5 mL	Wahlberg and Boman, 1979
Guinea pig	dermal	0.5 or 2.0 mL/3.1 cm²	single application	Death at 2 mL after 3 days, significantly decreased body weight gain at 0.5 mL	Wahlberg and Boman, 1979
Rabbit	intraperitoneal	1 or 2 mL/kg (945 or 1889 mg/kg)	single dose	Death within 3-4 days, reduced size of livers, clay-colored liver; fatty degeneration and necrosis of liver; increased blood sugar	Massmann, 1956
Cat	intraperitoneal	1 or 2 mL/kg (945 or 1889 mg/kg)	single dose	Death at ≥0.5 mL/kg, abnormal ECG, fatty degeneration and necrosis of liver	Massman, 1956
Cat	intravenous	1.5 mL of 57% solution	3 injections at 45-second intervals	Fatal hypotension and ventricular fibrillation	Pearl et al., 1978
Dog	intravenous	0.5 g/kg	single dose	Stimulated respiratory activity and myocardial contraction	Chanh et al., 1973

rats and aminopyrine and 7-ethoxycoumarin by S-9 fractions from phenobarbital-pretreated rats. No significant effect on p-nitroanisole and benzo[a]pyrene metabolism by S-9 fractions from rats pretreated with either inducer was observed.

In rats, Eben and Kimmerle (1976) found that ingestion of 2.0 g/kg ethanol before inhalation exposure to dimethylformamide at 87-209 ppm (260-625 mg/m³) for 2 hours or at 200 ppm (598 mg/m³) for 2 hours/day for 5 days resulted in delayed metabolism of dimethylformamide. Similar results were observed in dogs pretreated orally with 2.0 g/kg ethanol followed by inhalation exposure to dimethylformamide at ~230 ppm (688 mg/m³) for 2 hours, and in four humans ingesting 19 g ethanol/person before inhalation exposure to 50-80 ppm (149-239 mg/m³) dimethylformamide for 2 hours. The investigators noted that dimethylformamide inhibited the metabolism of ethanol in rats when the substances were administered concurrently for 5 days.

Several investigators have described Antabuse-type symptoms in workers who were exposed to dimethylformamide and had imbibed alcohol before or after exposure. Chivers (1978) reported the case of a 34-year-old maintenance fitter exposed for ~4 hours to <10-30 ppm (30-90 mg/m³) dimethylformamide vapors and also dermally to liquid dimethylformamide. Chest tightness and red blotchiness of the skin were noted when he drank as little as 0.5 pints of beer. Lyle et al. (1979) found that 19/102 men who worked with dimethylformamide reported 34 episodes of facial flushing, 26 of which occurred after alcohol ingestion.

Abdominal pain, nausea, vomiting, rashes on hands and forearms, clinical evidence of liver damage and epigastric tenderness have been associated with accidental exposure of workers to dimethylformamide (Potter, 1973; Chary, 1974; Reinl and Urban 1965).

In vitro treatment of murine rhabdomyosarcoma cells or human colon carcinoma cells with dimethylformamide resulted in induction of differentiation of the tumor cells (Calabresi et al., 1979; Dexter, 1977). When dimethylformamide-treated sarcoma cells were injected into CE/J mice, 3/17 mice developed tumors in 6 months; however, 21/21 mice injected with untreated cells died of tumors within 11-12 days. The *in vivo* and *in vitro* antitumor effects of dimethylformamide have been studied by numerous investigators and have been reviewed by U.S. EPA (1981).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute toxicity of dimethylformamide to aquatic biota has been studied in four species of freshwater fish and two species of freshwater invertebrates (Table 6-1). In addition, the acute toxicity of tetrachloroethylene and butylbenzyl phthalate with dimethylformamide as a carrier solvent was studied in one species of fish and one species of invertebrate, respectively.

Tonogai et al. (1982) reported 24- and 48-hour static TL_Ms of >1000 mg dimethylformamide/ℓ for the medaka, Oryzias latipes. The toxicity tests were performed with 10 fish/exposure vessel at 25°C in 2 ℓ of distilled water.

Dojlido (1979) reported the 24-hour static LC_{50} value of 1300 mg dimethylformamide/ℓ for the guppy, Poecilia reticulata. Tests were conducted according to standardized procedures. All nominal concentration test solutions were prepared with activated carbon treated tap water at pH 7.6-8.0; dissolved oxygen concentration was not reported.

The acute toxicity of dimethylformamide to the rainbow trout, Salmo gairdneri, was reported by Shubat et al. (1982). The 96-hour LC_{50} and NOEC values of 9860 and 7700 mg/ℓ, respectively, were presented. Test concentrations were maintained with a proportional diluter.

Shubat et al. (1982) also investigated the acute toxicity of tetrachloroethylene to rainbow trout with and without dimethylformamide as a carrier solvent. Ten fish were treated per exposure vessel, and solution concentrations were maintained with a proportional diluter and held at 12°C. During the test with dimethylformamide, concentrations of dimethylformamide up to 513 mg/ℓ were achieved. The 96-hour LC_{50} values for tetrachloroethylene and tetrachloroethylene with dimethylformamide were 4.99 and 5.84

TABLE 6-1

Acute Toxicity of Dimethylformamide to Freshwater Organisms

Species	Duration	Concentration	Method	Effect	Reference
Medaka					
Oryzias latipes	24 hours	>1,000 mg/L	static toxicity	TL_m	Tonogai et al., 1982
	48 hours	>1,000 mg/L	static toxicity	TL_m	
Guppy					
Poecilia reticulata	24 hours	1,300 mg/L	static toxicity	LC_{50}	Bojlido, 1979
Rainbow trout					
Salmo gairdneri	96 hours	9,860 mg/L	proportional diluter	LC_{50}	University of Wisconsin, 1978
	96 hours	7,700 mg/L	proportional diluter	NOEC	
Photobacterium phosphoreum	5 minutes	20,000 mg/L	microtox test	EC_{50}	Curtis et al., 1982
Crustacean					
Daphnia magna	24 hours	17,000 µL/L	static toxicity	LC_{50}	LeBlanc and Surprenant, 1983
	48 hours	13,000 µL/L	static toxicity	LC_{50}	
	28 days	2,500 µL/L	proportional diluter	MATC	
	48 hours	10,800 mg/L	static toxicity	EC_{50}	Barera and Adams, 1983
	48 hours	6,000 mg/L	static toxicity	NOEC	
Mosquito larvae					
Aedes aegypti	4 hours	72,000 µL/L	static toxicity	LC_{50}	Kramer et al., 1983
Green alga					
Selenastrum capricornutum	14 days	500 µL/L	algal assay bottle test	NOEC	Hughes and Vilkas, 1983
Scenedesmus quadricauda	NR	0.04 mg/L	NR	"safe dose"	Lebkowska and Rzechowska, 1980
	NR	7.4 mg/L	NR	"harmful dose"	

NR = Not reported

mg/ℓ, respectively. It was concluded that dimethylformamide, when proportionally diluted and used at or below the maximum recommended level (472 mg/ℓ dimethylformamide, ASTM, 1980), did not significantly influence the acute toxicity of tetrachloroethylene to rainbow trout.

Curtis et al. (1982) conducted a Microtox test, a rapid screening technique that measures the decrease in natural light emission from the luminescent bacteria, Photobacterium phosphoreum, in response to a contaminant, in order to estimate the acute toxicity of dimethylformamide to the fathead minnow, Pimephales promelas. The 5-minute EC_{50}, the concentration that causes a 50% reduction in light output, was determined to be 20,000 mg/ℓ dimethylformamide. The authors reported that these results are in close agreement with unpublished LC_{50} values obtained from acute toxicity tests performed with fathead minnows and dimethylformamide.

LeBlanc and Surprenant (1983) reported 24- and 48-hour static EC_{50} values of 16 and 12 g dimethylformamide/ℓ, respectively, for the daphnid, Daphnia magna. Nominal test concentrations were prepared in triplicate from soft well water maintained at 21±1°C; the solutions were not aerated.

Barera and Adams (1983) investigated the acute toxicity of dimethylformamide as well as the influence of dimethylformamide on the acute toxicity of butylbenzyl phthalate to the daphnid, Daphnia magna, using standardized procedures. They reported 48-hour static EC_{50} and NOEC values of 18.8 and 6.0 g/ℓ, respectively, for daphnids exposed to dimethylformamide and 48-hour static EC_{50} values of 1.0 and 1.8 mg/ℓ for daphnids exposed to butylbenzyl phthalate and butylbenzyl phthalate with dimethylformamide as a solvent, respectively. It was concluded that dimethylformamide did not influence the toxicity of butylbenzyl phthalate.

Kramer et al. (1983) reported the 4-hour static LC_{50} value of 72,000 µℓ dimethylformamide/ℓ for the mosquito larvae, Aedes aegypti; the test was performed three times and the result is expressed as an average.

6.2. CHRONIC TOXICITY

LeBlanc and Surprenant (1983) investigated the chronic toxicity of dimethylformamide to Daphnia magna. Solvent concentrations, prepared as nominal concentrations (600-10,000 µℓ/ℓ), were maintained with 200 mℓ proportional diluters. Twenty daphnids were randomly distributed to each aquarium upon initiation of the test. Adult survival and reproductive success were monitored throughout the 28-day exposure period. The MATC for daphnids exposed to dimethylformamide was determined to be between 1200 and 2500 µℓ/ℓ.

6.3. PLANT EFFECTS

Hughes and Vilkas (1983) investigated the toxic effects of dimethylformamide on the green alga, Selenastrum capricornutum, using the algal assay bottle test. Nominal concentrations [0 (control) to 1.0 mℓ/ℓ] of dimethylformamide were added to 1-week-old cultures in 250 mℓ Erlenmeyer flasks fitted with foam stoppers. Cultures were incubated at 24±2°C for 14 days in a thermostatically controlled incubater-shaker. Growth of the test alga, expressed as maximum standing crop, was determined on days 0, 1, 2, 3, 5, 7, 9, 11 and 14 (Table 6-2). The NOEC, the highest concentration tested that had no significant effect upon maximum standing crop (cell/mℓ or dry weight, mg/ℓ), for S. capricornutum exposed to dimethylformamide was 0.5 mℓ/ℓ (see Table 6-1).

Lebkowska and Rzechowska (1980) reported the safe concentration of ~10 mg/ℓ dimethylformamide to the alga, Scenedesmus quadricauda; however, no information regarding experimental procedures was provided.

TABLE 6-2

Maximum Standing Crop of Selenastrum capricornutum Exposed to Dimethylformamide[a]

Duration of Exposure (days)	Concentration (mℓ/ℓ)	Mean Maximum Standing Crop[b] (mg/ℓ)
9	0 (control)	127.9
7-9	0.10	132.4
7-9	0.18	136.9
7-9	0.32	131.7
7-9	0.56	137.9
7	1.0	149.4

[a]Source: Hughes and Vilkas, 1983

[b]Dry weight

6.4. RESIDUES

Pertinent data regarding the residues of dimethylformamide in aquatic organisms could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1984) has adopted a TWA-TLV for occupational exposure to dimethylformamide of 10 ppm (30 mg/m³) with a "skin" notation, indicating that the dermal route contributes to the overall exposure. The adopted TLV was recommended by ACGIH (1980) based primarily on the experience of E.I. Du Pont de Nemours and Co., Inc. (n.d.) that no complaints of worker illness and no abnormal liver function tests were reported for several hundred workers in two plants where skin contact is prevented, air concentrations are kept at approximately one-half the TLV and urine samples of workers are monitored regularly for metabolites of dimethylformamide.

OSHA also adopted a TWA-TLV of 10 ppm (30 mg/m³) for occupational exposure to dimethylformamide (Code of Federal Regulations, 1985). The ACGIH (1985) also adopted an STEL of 20 ppm (60 mg/m³) for dimethylformamide based on the recommendation of ACGIH (1980); however, ACGIH (1985) intends to delete the STEL.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of dimethylformamide could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Dimethylformamide has not been studied adequately for carcinogenicity; testing by the National Toxicology Program has been deferred (NTP, 1985). Oral administration at 75-150 mg/kg/day for 250-500 days or subcutaneous injection of 200-400 mg/kg/week for up to 50 weeks did not result in tumor induction in rats (Druckrey et al., 1967). Rats injected intraperitoneally with 0.1 mL/rat/week (39 mg/kg/day, using the density as given in Section 1.2., assuming that a rat weighs 0.35 kg and dividing by 7 days/week) for 10 weeks developed malignant and benign tumors in the abdominal cavity and reproductive tract at incidences of 9/18 for males and 11/19 for females (Kommineni, 1973). The incidence of tumors in controls was not reported, however, precluding evaluation of the incidence in treated rats.

Dimethylformamide has been studied extensively for mutagenicity and genotoxicity in a variety of assay systems (see Table 5-1). With the exception of a few false positive results, the overwhelming evidence indicates that dimethylformamide is not mutagenic or genotoxic.

Dimethylformamide was teratogenic, fetotoxic and maternotoxic when administered by gavage to pregnant rabbits on days 6-18 of gestation (Merkle and Zeller, 1980). At the high dose (200 µL/kg/day or 188.9 mg/kg/day, using the density of dimethylformamide as presented in Section 1.2.), dams had reduced food intake and weight gain, a statistically significant decrease ($p \leq 0.05$) in mean fetal weight and significant ($p < 0.05$) increases in the percentage of malformed live fetuses/litter and the percentage of litters with malformed fetuses. Malformations at the high dose consisted of hydrocephalus, abnormally positioned extremities, simple eventration,

umbilical hernia, exophthalmos and cleft palate. A few fetuses at the lower doses (43.8 and 64.3 mg/kg/day) had hydrocephalus, but these results were not significantly different from controls.

Inhalation teratology studies have also been conducted in rats (Keller and Lewis, 1981; Kimmerle and Machemer, 1975; Sheveleva and Osina, 1973; Sheveleva et al., 1979; Gofmekler et al., 1970). Inhalation concentrations ranged from 0.01-900 mg/m^3, individual exposures ranged from 4 hours/day to continuous and from gestational days 6-15 to throughout the gestational period. No evidence of teratogenicity was associated with these exposures. Calculation of equivalent oral doses by standard methods indicates that fetal toxicity (decreased fetal weight, ossification variations, embryomortality) occurred at doses below those in the gavage study, as well as at doses that were toxic to dams; however, calculations of equivalent oral doses from inhalation exposures involve assumptions that do not account for the first pass metabolism that occurs in the liver after oral administration. As noted in Section 4.3., dimethylformamide is metabolized extensively in the liver; therefore, data obtained from oral administration are more appropriate than data from inhalaton exposure for use in quantitative risk assessment. Dermal application of dimethylformamide to pregnant rats on various days during gestation resulted in increased embryomortality only at doses that were toxic to dams (1200-2400 mg/kg/day on 3 gestational days) (Stula and Krauss, 1977). Although dimethylformamide is readily absorbed by the dermal route (see Section 4.1.), no effects were observed in rabbits treated dermally with 200 mg/kg/day on days 8-16 of gestation. It is not possible to calculate the equivalent oral doses. Occupational exposure to dimethylformamide has been associated with increased rate of spontaneous abortion (Farquharson et al., 1983; Schottek, 1972).

Data regarding the effects of long-term oral exposure to dimethylformamide were available from subchronic studies. Dietary administration of dimethylformamide to mice at 160, 540 or 1850 ppm for 119 days resulted in significantly ($p<0.05$) increased weights of thyroids, adrenals and liver at 1850 ppm in males and females and liver at 540 ppm in females (Becci et al., 1983). The only histological finding was slight hepatocytomegaly in most mice receiving 1850 ppm. The dietary levels were equivalent to dosages of 22, 70 and 246 mg/kg/day for males and 28, 96 and 326 mg/kg/day for females, as determined by the investigators from food consumption and weight gain data. In rats treated at dietary levels of 215, 750 and 2500 ppm for 104 days, there was a decreased mean body weight gain associated with reduced food consumption and significantly ($p<0.05$) increased relative weights of the brain and testes at 2500 ppm. The relative liver weight was significantly ($p<0.05$) increased at 750 ppm in females and at 2500 ppm in males and females (Becci et al., 1983). No histological changes were found in rats. The dietary levels were equivalent to dosages of 18, 61 and 210 mg/kg/day for male rats and 20, 69 and 235 mg/kg/day for female rats, as determined by the investigators. Dietary administration of dimethylformamide to rats at 5000 ppm for 90 days resulted in slight liver damage (not otherwise specified), anemia, leukocytosis and increased cholesterol levels (Du Pont, 1968; E.I. Du Pont de Nemours and Company, 1980). No effects were observed at 200 and 1000 ppm. The 200, 1000 and 5000 ppm dietary levels are equivalent to dosages of 20, 100 and 500 mg/kg/day, respectively, assuming that a young growing rat in a subchronic study consumes a daily amount of food equal to 10% of its body weight (Mitruka et al., 1976).

Savolainen (1981) found that dimethylformamide in the drinking water of rats at concentrations of ~100, 500 and 1000 mg/ℓ for 2 and 7 weeks resulted in time- and dose-related biochemical changes in the homogenized cerebrum and in isolated cerebral glial cells (see Section 5.5. for specific changes). The investigators suggested that formic acid, a minor metabolite of dimethylformamide (see Section 4.3.), may interfere with cerebral cellular respiration; however, no histological examinations were performed and no behavioral effects were observed. The investigator determined total doses in mmol/kg (see Section 5.5.), equivalent to 7.0, 35.8 and 65.5 mg/kg/day after 7 weeks. In rats treated as above, time- and dose-related altered activities of liver and kidney microsomal enzymes were observed at ≥100 mg/ℓ (Elovaaro et al., 1983). Aldehyde metabolism was inhibited at ≥500 mg/ℓ, and there was a dose-related significant increase in relative liver weight at ≥100 mg/ℓ. Histological examination was not performed and no signs of toxicity were observed. Elovaara et al. (1983) did not calculate doses, but rats of the same strain and age were used as in the study of Savolainen (1981).

Drinking water concentrations of ≥10,000 mg/ℓ (≥100,000 mg/kg, total dose determined by the investigator or ≥500 mg/kg/day) were fatal to gerbils, with time to 50% mortality decreasing from 200 days at 10,000 mg/ℓ to 3 days at 66,000 mg/ℓ (Llewellyn et al. 1974). Gerbils that died had necrotic lesions in the livers.

The effects of subchronic inhalation exposure to dimethylformamide has been studied in a variety of species (Hofmann, 1960; Clayton et al., 1963; Massmann, 1955, 1956; Arena et al., 1982; Odoshashvili, 1963, Cruz and Maccioni, 1978; Costa et al., 1978; Germanova et al., 1979; Schottek, 1970).

Inhalation concentrations ranged from 0.5-2989 mg/m³ for durations of 0.5-8 hours/day and from 5 days to 10 months. Such effects as functional and histopathological changes in the liver, pancreas, spleen, kidney, adrenals and thymus were observed in dogs, rabbits, guinea pigs, rats and mice. Effects on the myocardium were observed in dogs and rabbits, blood pressure changes were observed in dogs and gastroenteritis and pulmonary effects were observed in rats. Calculation of equivalent oral doses from the inhalation exposures by standard methods indicates that some of these effects occurred at doses below actual oral doses at which no adverse effects were observed. For reasons discussed previously, however, quantitative risk assessment is more appropriately based on oral exposure data.

Occupational exposure to dimethylformamide has been associated with hematological effects, gastroduodenal hyperdyskinesia, gastritis (Di Lorenzo and Grazioli, 1972), dyspepsia, diarrhea and alcohol intolerance (Paoletti and Iannacone, 1982). Exposure levels were not reported.

Although the study by Kommineni (1973) suggests that diemthylformamide is tumorigenic in rats, administration of the compound was by intraperitoneal injection and tumor incidences for control rats were not reported, precluding the calculation of a q_1^*. Therefore, a tentative ADI derived from the subchronic oral studies is recommended until definitive data regarding carcinogenicity become available. The studies by Elovaara et al. (1983), Becci et al. (1983) and E.I. Du Pont de Nemours and Company (1980) comprise an appropriate data base obtained from oral administration, the most relevant route of exposure, for effects of dimethylformamide on the liver. Since dimethylformamide, a small molecule, is extensively metabolized in the liver following GI absorption, the liver is expected to be a primary target organ for toxicity. At drinking water levels equivalent to

7.0, 35.8 and 65.5 mg/kg/day, liver enzymes were affected and liver weight was increased in rats (Elovaara et al., 1983). In the dietary studies of Becci et al. (1983), the relative liver weight of mice was increased at doses of 96-326 mg/kg/day. The only histological finding was enlargement of hepatocytes, which is possibly due to enzyme induction, at 246 and 326 mg/kg/day in males and females, respectively. Relative liver weights of rats were also increased at dietary levels of 69-235 mg/kg/day (Becci et al., 1983). Becci et al. (1983) also found increases in other organ weights, but no evidence of histopathology was observed in these organs and the biological significance of these elevated organ weights is doubtful. The dietary study of E.I. Du Pont de Nemours and Company (1980) reported histological evidence of liver damage in rats at 500 mg/kg/day. Other effects included anemia and leukocytosis. Savolainen (1981) found biochemical effects in the brains of rats after 2 and 7 weeks at doses lower than those in the longer-term studies; however, in the absence of histological examination and behavioral effects, these effects do not appear to be adverse. In the absence of histopathological evidence, enzyme changes in the liver and increased liver weights also cannot be considered adverse. The LOAEL for hepatoxicity following oral exposure to dimethylformamide appears to be 500 mg/kg/day, at which treatment-related hematological effects were also observed (E.I. DuPont de Nemours and Company, 1980). The next lowest dose in these subchronic oral studies, 326 mg/kg/day (Becci et al., 1983), could be considered the highest NOAEL; however, dimethylformamide was teratogenic and fetotoxic when administered by gavage to pregnant rabbits at 188.9 mg/kg/day on days 6-18 of gestation (Merkle and Zeller, 1980). The dose was also mildly toxic to the dams, resulting in decreased food consumption and body weight gain. Reduced food consumption and body

weight was also observed at the high-dose level in male and female rats (210 and 235 mg/kg/day), but not mice, in the dietary studies by Becci et al. (1983). No effects were observed at a dose of 100 mg/kg/day in the study reported by E.I. Du Pont de Nemours and Company (1980). At the middle doses in the dietary studies by Becci et al. (1983), (70 and 96 mg/kg/day for male and female mice, respectively, and 61 and 69 mg/kg/day for male and female rats, respectively), no treatment-related adverse effects were observed. The highest of these doses, 100 mg/kg/day or 96 mg/kg/day, could be considered a NOAEL. Using the NOAEL of 96 mg/kg/day (Becci et al., 1983) an ADI of 0.096 mg/kg/day or 6.72 mg/day for a 70 kg man can be derived by applying an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 to protect the most sensitive individuals of the human population and 10 to approximate chronic exposure). The dose of 64.3 mg/kg/day in the teratology study was not teratogenic, fetotoxic or maternotoxic in rabbits (Merkel and Zeller, 1980); however, an ADI of 0.64 mg/kg/day calculated from this NOAEL by applying an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect for the most sensitive individuals of the human population) may not provide adequate protection for chronic toxicity of dimethylformamide. Therefore, until further information regarding the carcinogenicity of dimethylformamide becomes available, an ADI of 0.096 mg/kg/day is provisionally recommended to protect humans from the teratogenic, fetotoxic and hepatotoxic effects of dimethylformamide.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Data regarding the effects of long-term oral and inhalation exposure of animals to dimethylformamide were available from the subchronic studies discussed in Section 5.5.; in addition, several teratology studies were available and were discussed in Section 5.3. The studies appropriate for consideration in the derivation of the RQ are summarized in Table 9-1. The method of determining doses in units of mg/kg/day from the nominal exposures are given in the footnotes to Table 9-1; however, further clarification of doses calculated from inhalation exposures is required. The daily breathing rates for the various species used in the calculation of the doses were 0.223 m^3/day for rats and 0.039 m^3/day for mice (U.S. EPA, 1980), 4.3 m^3/day for dogs, 1.2 m^3/day for cats, 2.0 m^3/day for rabbits and 0.40 m^3/day for guinea pigs (Durkin, 1985). Assigned animal body weights were 0.35 kg for rats and 0.03 kg for mice (U.S. EPA, 1980), 12.7 kg for dogs, 3.0 kg for cats, 3.8 kg for rabbits and 0.84 kg for guinea pigs (Durkin, 1985).

Data used to calculate MEDs and CSs are summarized in Table 9-2. To calculate the MEDs, the animal doses were multiplied by the cube root of the ratio of the animal body weight to the human body weight (70 kg) and multiplied by 70 kg to express the MED in units of mg/day for a 70 kg human. For subchronic studies, the doses were divided by an uncertainty factor of 10 to approximate chronic exposures. No such adjustment was made for teratology studies.

The lowest dose in the oral studies at which organ weight changes were observed was 7.0 mg/kg/day, in the study of Elovaara et al. (1983) (see Table 9-1). The MED is 8.4 mg/day, corresponding to an RV_d of 4.1. Organ

TABLE 9-1

Toxicity Summary for Dimethylformamide

Route	Species/ Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Oral	mouse/CD-1	M	30/group	diet	99.9%	160, 540 and 1850 ppm for 119 days	22, 70 and 246[a]	Significantly increased absolute and relative liver weight; slight hepatocytomegaly at 246 mg/kg/day	Becci et al., 1983
Oral	mouse/CD-1	F	30/group	diet	99.9%	160, 540 and 1850 ppm for 119 days	28, 96 and 326[a]	Significantly increased absolute and relative weight of thymus and adrenals at 326 mg/kg/day, of liver at ≥96 mg/kg/day; slight hepatocytomegaly at 326 mg/kg/day	Becci et al., 1983
Oral	rat/Wistar	M	25/group	diet	99.9%	215, 750 and 2500 ppm for 104 days	18, 61 and 210[a]	Significantly increased absolute weights of brain and testis and absolute and relative weight of liver at 210 mg/kg/day	Becci et al., 1983
Oral	rat/Wistar	F	25/group	diet	99.9%	215, 750 and 2500 ppm for 104 days	20, 69 and 235[a]	Significantly increased absolute and relative weight of liver at ≥69 mg/kg/day	Becci et al., 1983
Oral	rat/NR	M,F	NR	diet	NR	200, 1000 and 5000 ppm for 90 days	20, 100 and 500[b]	Liver damage, anemia, leukocytosis and hypercholesterolemia at 500 mg/kg/day	Du Pont, 1968; E.I. Du Pont de Nemours and Company, 1980
Oral	rat/Wistar	M	10/group	drinking water	99.5%	1.4, 6.8 or 13.7 mmol/L (102.3, 497.0 or 1001 mg/L) for 7 weeks	7.0, 35.0 and 65.5[c]	Significant changes in brain biochemistry at ≥7.0 mg/kg/day; no behavioral effects	Savolainen, 1981
Oral	rat/Wistar	M	10/group	drinking water	99.5%	100, 500 or 1000 mg/L for 7 weeks	7.0, 35.0 and 65.5[d]	Dose-related significantly increased relative liver weight at ≥7.0; dose-related changes in liver and kidney metabolizing enzymes at ≥7.0 mg/kg/day	Elovaara et al., 1983
Oral	rat/NR	NR	NR	NR	NR	200 mg/kg/day, 4 weeks	200	Decreased level of cytochrome P450 and demethylase activity of liver	Martinchuk et al., 1984

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TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Oral	gerbil/ Mongolian	F	12/group	drinking water	analytical grade	≥10,000 mg/ℓ for ≤200 days	>500[c]	Time to 50% mortality decreasing from 200 days at 10,000 mg/ℓ to 3 days at 66,000 mg/ℓ, liver necrosis	Llewellyn et al., 1974
Oral	guinea pig/NR	NR	NR	NR	NR	400 mg/kg/day, 14 days	400	Decreased ascorbic acid content of the liver, adrenals and liver, decreased cytochrome P450 of liver	Leshik and Feoktistova, 1984
Oral (gavage)	rabbit/ Russian	F	11-18 group	aqueous solution	technical product	0, 46.4, 68.1 and 200 µℓ/kg/day on days 6-18 of gestation	43.8, 64.3 and 188.9[g]	Maternal toxicity (decreased body weight and food consumption), fetotoxicity (reduced fetal body weight), teratogenicity(malformed /etuses) at 188.9 mg/kg/day	Merkle and Zeller, 1980
Inhalation	dog rabbit guinea pig rat mouse	M M,F M M,F F	4 2/sex 10 10/sex 11	vapor	NR	TWA of 56.6 ppm (169 mg/m³) 6 hours/day, 5 days/week, 11.8 weeks[g]	10.2[f] 15.9[f] 14.4[f] 19.2[f] 39.2[f]	Functional and histopathologic changes in liver, pancreas, spleen, kidneys, adrenals and thymus; dogs had degenerative changes in the heart	Clayton et al., 1963
Inhalation	dog/NR	M	4	vapor	NR	20 ppm (60 mg/m³) 6 hours/day, 5 days/week, 107 exposures	3.6[f]	Decreases in blood pressure and heart rate during the exposure period that became more pronounced with time	Clayton et al., 1963
Inhalation	rat/NR	NR	16/group	vapor	NR	100, 230 and 450 ppm (299, 688 and 1345 mg/m³) 8 hours/day, 6 days/week for 120 days	54, 125 and 245[f]	38% mortality in 56 days at 245 mg/kg/day; necrosis and fatty degeneration of the liver at ≥54 mg/kg/day	Massmann, 1955, 1956
Inhalation	cat/NR	NR	2/group	vapor	NR	100, 230 and 450 ppm (299, 688 and 1345 mg/m³), 8 hours/day, 6 days/week for 120 days	34, 79 and 154[f]	Both cats died at 147 mg/kg/day; necrosis and fatty degeneration of the liver at ≥32 mg/kg/day	Massmann, 1955, 1956
Inhalation	rabbit/NR	NR	NR	vapor	NR	40 ppm (120 mg/m³) 8 hours/day for 50 days	21.1[f]	Heart damage	Arena et al., 1982

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Inhalation	rat/NR	NR	NR	vapor	NR	0.5 and 10 mg/m³ continuous for 2 months	0.3] and 6.4[f]	Decreased cholinesterase levels, reduced elimination of coproporphyrin	Odoshashvili, 1963
Inhalation	rat/ Sprague-Dawley	F	19/group	vapor	NR	32 and 301 ppm (96 and 900 mg/m³) 6 hours/day on days 6-15 of gestation	15 and 143[f]	Reduced weight gain of dams, significantly decreased mean fetal weight, significantly increased incidence of ossification variations at 143 mg/kg/day	Keller and Lewis, 1981
Inhalation	rat/NR	F	22 or 23	vapor	NR	18 or 172 ppm (54 or 514 mg/m³), 6 hours/day, days 6-15 of gestation	3 or 27[f]	Decreased fetal body weight at 27 mg/kg/day, no maternal toxicity	Kimmerle and Machemer, 1975
Inhalation	rat/NR	F	NR	vapor	NR	10.7, 50 or 600 mg/m³, 4 hours/ day for 20 gestational days	1.13, 5 or 64[f]	Increased embryonic mortality at >1.13 mg/kg/day, decreased fetal growth at 5 and 64 mg/kg/day	Sheveleva and Osina, 1973; Sheveleva et al., 1979
Inhalation	rat/NR	F	12/group	vapor	NR	0.01-500 mg/m³ throughout gestation	NC[h]	At 500 mg/m³, all rats aborted, 5/12 died; structural changes in fetuses at unspecified concentrations	Gofmekler et al., 1970

[a]Equivalent doses provided by Becci et al. (1983)

[b]Doses calculated assuming that young growing rats in a subchronic study consume a daily amount of food equal to 10% of the body weight (Mitruka et al., 1976)

[c]Doses calculated from information provided by the investigators

[d]Doses were assumed to be the same as the doses in the Savolainen (1981) study

[e]Doses were calculated using the density of dimethylformamide as given in Section 1.2.

[f]Dose calculated by expanding the exposures over a 24-hour day and 7-day week, when appropriate, and by multiplying by the animal daily breathing rate and dividing by the animal body weight (see text). Absorption efficiency was assumed to be 100%.

[g]Actual exposure was 23 ppm (69 mg/m³) for 5.5 hours/day followed by 426 ppm (1273 mg/m³) for 0.5 hours/day.

[h]A dose could not be calculated because it was not clear if exposure was continuous or not.

NR = Not reported; NC = not calculated

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TABLE 9-2

Composite Scores for Toxicity of Dimethylformamide

Route	Species	Dose/Exposure	Human MEB* (mg/day)	RV_d	Effect	RV_e	CS	MF	Reference
Oral	rat	7 mg/kg/day for 7 weeks	8.4*	4.1	Increased liver weight, biochemical changes in liver and kidney	4	16.4	1000	Elovaara et al., 1983
Oral	rat	500 mg/kg/day for 90 days	598*	1.3	Liver damage, anemia, leukocytosis, hyperchloesterolemia	6	7.8	1000	Du Pont, 1968; E.I. Du Pont de Nemours and Company, 1980
Oral	rabbit	188.9 mg/kg/day on days 6-18 of gestation	5007	1	Fetotoxicity and teratogenicity with maternal toxicity	9	9	1000	Merkel and Zeller, 1980
Inhalation	dog	10.2 mg/kg/day, 11.8 weeks	40.4*	3.1	Functional and histological changes in liver, pancreas, spleen, kidneys, adrenal, thymus and heart	7	21.7	100	Clayton et al., 1963
Inhalation	dog	3.6 mg/kg/day, 107 days	14.3*	3.8	Changes in blood pressures and heart rate	2	7.6	1000	Clayton et al., 1963
Inhalation	rat	0.31 mg/kg/day, 2 months	0.37*	6.1	Decreased cholinesterase levels, reduced elimination of coproporphyrin	1	6.1	1000	Odoshahvili, 1963
Inhalation	rat	27 mg/kg/day, days 6-15 of gestation	323	1.7	Fetotoxicity	7	11.9	1000	Kimmerle and Machemer, 1975

*The exposures were divided by a factor of 10 to approximate chronic exposure.

weight changes warrant an RV_e of 4. Multiplying the RV_d by the RV_e results in a CS of 16.4, corresponding to an RQ of 1000. Hepatocytomegaly was observed at higher doses (Becci et al., 1983), but the RV_e for such an effect is also 4. Since the CS for this effect would be lower than 16.4, the effect is not ranked on Table 9-2. As seen on Table 9-1, biochemical changes were also observed at 7.0 mg/kg/day and at higher doses (Elovaara et al., 1983; Savolainen, 1981; Martinchuk et al., 1984; Leshik and Feoktistova, 1984), but the RV_e for biochemical effects is 1 or 2, which would also result in lower CSs. The lowest oral dose at which histopathological evidence of liver damage was observed was 500 mg/kg/day (Du Pont, 1968; E.I. Du Pont de Nemours and Company, 1980). The MED is 598 mg/day, corresponding to an RV_d of 1.3. Liver damage warrants an RV_e of 6; the CS is 7.8, corresponding to an RQ of 1000. The other effects seen at 500 mg/kg/day would warrant RV_es <6. Fetotoxicity and teratogenicity were observed at a dose that was toxic to dams (Merkle and Zeller, 1980); therefore, these effects have an RV_e of 9. The dose of 188.9 mg/kg/day is equivalent to a human MED of 1; the CS is 9 corresponding to an RQ of 1000. The early mortality of gerbils observed by Llewellyn et al. (1974) (see Table 9-1) cannot be ranked because the effect was an acute response to relatively high exposures.

For the subchronic inhalation studies, the experiments of Clayton et al. (1963) provide the lowest doses for functional and histopathological changes (see Table 9-1). These changes were seen in all species at the same inhalation concentration, but the lowest dose, 10.2 mg/kg/day, resulted from the calculation using the inhalation rates and body weight of dogs. The MED is 40.4 mg/day corresponding to an RV_d of 3.1. The effects warrant an RV_e of 7; the CS is 21.7, corresponding to an RQ of 100. Clayton et al. (1963)

also observed decreases in blood pressure and heart rate of dogs during exposure to lower concentrations. The changes became more pronounced as exposures were repeated. The equivalent dose was calculated to be 3.6 mg/kg/day and the MED is 14.3 mg/day, corresponding to an RV_d of 3.8. The effects warrant an RV_e of 2, resulting in a CS of 7.6 and an RQ of 1000.

Odoshashvili (1963) observed biochemical changes at relatively low doses. Although available details of this study were limited, a CS of 6.1, corresponding to an RQ of 1000, was calculated (see Table 9-2). The early mortality observed in cats and rats by Massmann (1955, 1956) was not ranked because it was an acute response to a relatively high exposure. Heart damage was observed by Arena et al. (1982) in rabbits, but the dose was higher than that at which heart damage was observed in dogs; therefore, no CS was calculated for these data.

Inhalation teratology studies reported embryotoxic and fetotoxic effects in rats (see Table 9-1). Although Sheveleva and Osina (1973) and Sheveleva et al. (1979) reported embryomortality in rats at exposures equivalent to 1.13 mg/kg/day, the data were available only from abstracts of these Russian studies and details were limited. Furthermore, Keller and Lewis (1981) and Kimmerle and Machemer (1975) did not observe embryotoxicity in rats at higher exposure levels. The lowest dose in these studies at which fetotoxic effects were observed is 27 mg/kg/day in rats that were treated during gestation (Kimmerle and Machemer, 1975). The MED is 323 mg/day, corresponding to an RQ of 1.7. Fetotoxicity warrants an RV_e of 7. The CS is 11.9, corresponding to an RQ of 1000 (see Table 9-2). No MED could be calculated for the fetotoxicity study of Gofmekler et al. (1970) because data are insufficient to calculate a dose. As seen from Table 9-2, the highest CS (21.7) was obtained from the inhalation study of Clayton et al. (1963). The RQ of 100 is recommended for dimethylformamide (Table 9-3).

TABLE 9-3

Dimethylformamide

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose:*	40.4 mg/day
Effect:	functional and histopathological changes in liver, pancreas, spleen, kidneys, adrenals, thymus and heart
Reference:	Clayton et al., 1963
RV_d:	3.1
RV_e	7
Composite Score:	21.7
RQ:	100

*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Testing of dimethylformamide for carcinogenicity by the National Toxicology Program has been deferred (NTP, 1985). Druckrey et al. (1967) found that dimethylformamide did not induce tumors in rats treated orally at 75-150 mg/kg for 250-500 days (until a total dose of 38 g/kg had been reached) or subcutaneously at 200-400 mg/kg/day (until a total dose of 8-20 g/kg had been reached).

Komminent (1973) reported a high incidence of malignant and benign tumors in the GI tract, the adrenals and the reproductive organs of 18 male and 19 female MCR rats treated intraperitoneally with dimethylformamide at 0.1 ml/rat/week. After 10 weeks, 9/18 males developed 13 tumors (4 pheochromocytomas of the adrenal medulla, 1 stomach carcinoma, 1 colon sarcoma, 1 embryonal cell carcinoma of the testis and 6 benign tumors in unspecified organs and 11/19 females developed 17 tumors (9 malignant and 8 benign). The tumors observed in females were 2 adenocarcinomas and a leiomyoma of the colon, 1 squamous cell carcinoma of the rectum, 1 adenomocarcinoma each of the adrenal cortex and pancreas and 11 tumors of unspecified type in the reproductive organs. The study had been designed to test for the carcinogenicity of aflatoxin dissolved in dimethylformamide and the dimethylformamide-treated group was intended as a solvent control. For the untreated control group (14 male and 14 female rats), the incidence of tumors was reported to be consistent with "earlier reported results"; however, the actual incidences were not reported. Because the incidence of tumors in untreated controls was not provided and because the chemical was administered intraperitoneally rather than by a natural route, it is not possible to derive a potency factor.

Using the IARC criteria for evaluating the overall weight of evidence for carcinogenicity, dimethylformamide is most appropriately placed in Group 3, that is, it cannot be classified as to its carcinogenicity for humans. Based on the U.S. EPA Proposed Guidelines for Carcinogen Risk Assessment, dimethylformamide can be classified as a Group D, not classifiable as to human carcinogenicity. This category is used for chemicals with inadequate human and animal evidence of carcinogenicity. Therefore, no direct ranking for carcinogenicity is possible using the hazard ranking scheme under CERCLA.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in April, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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In addition, FYI-OTS-0479-0030 was obtained and reviewed; also, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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